VOLUME 52 NUMBER 11 NOVEMBER 1959

PROCEEDINGS
of the
ROYAL SOCIETY OF MEDICINE

Published by
THE ROYAL SOCIETY OF MEDICINE, 1 WIMPOLE STREET, LONDON, W.1

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All correspondence to

THE HONORARY EDITORS, 1, WIMPOLE STREET, LONDON, W.1

(Tel.: LANgham 2070)

Distributing Agents:

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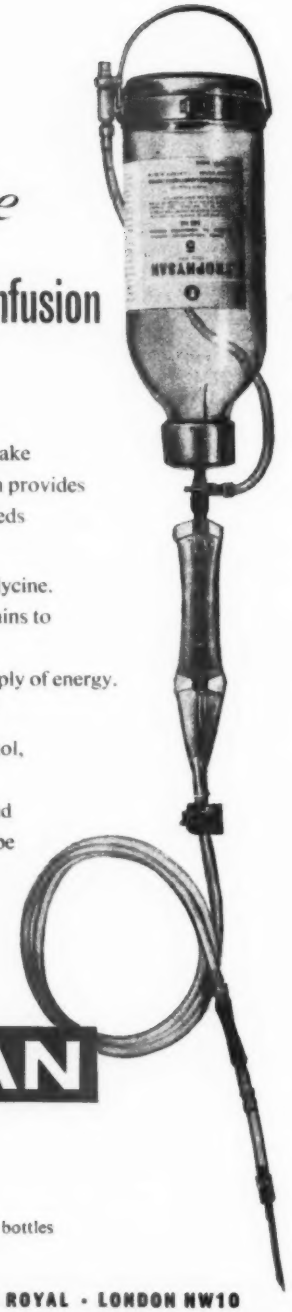

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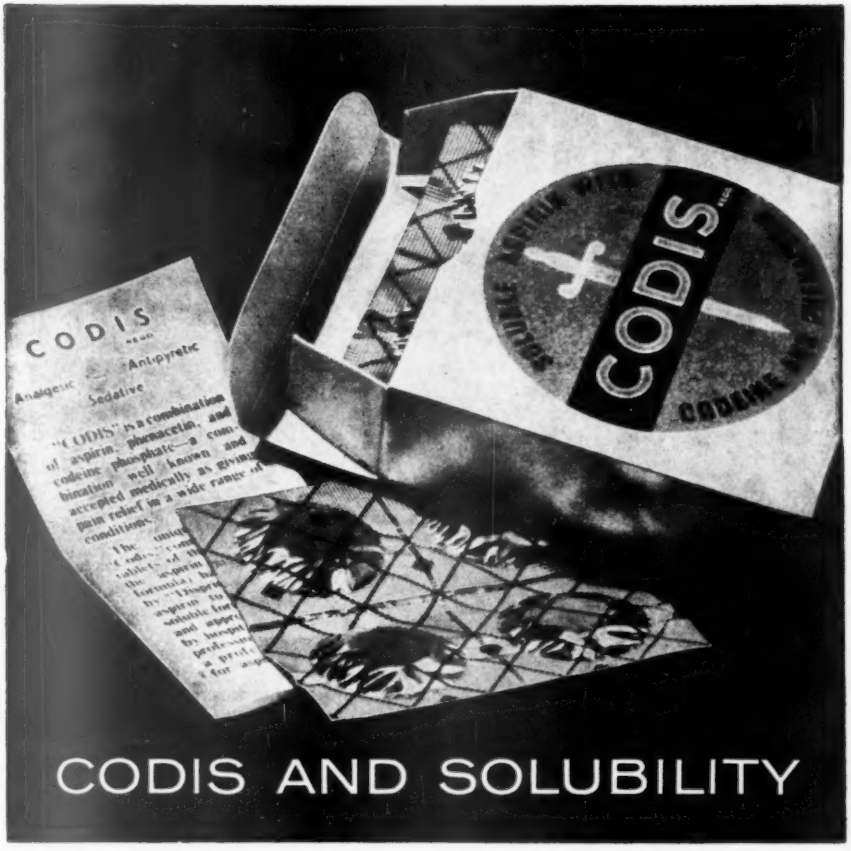

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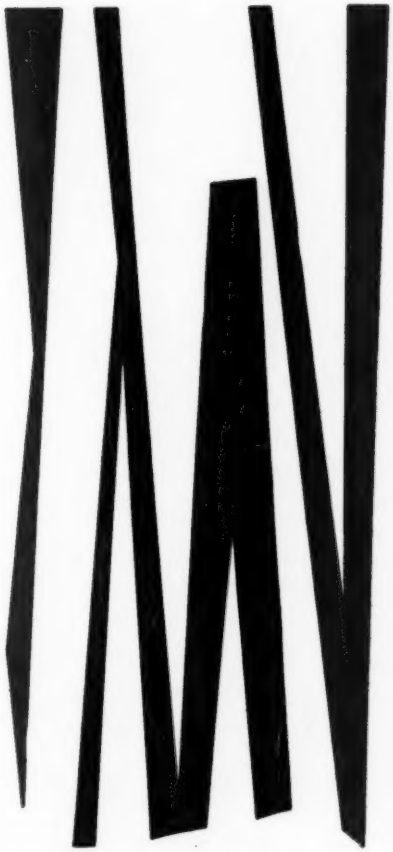

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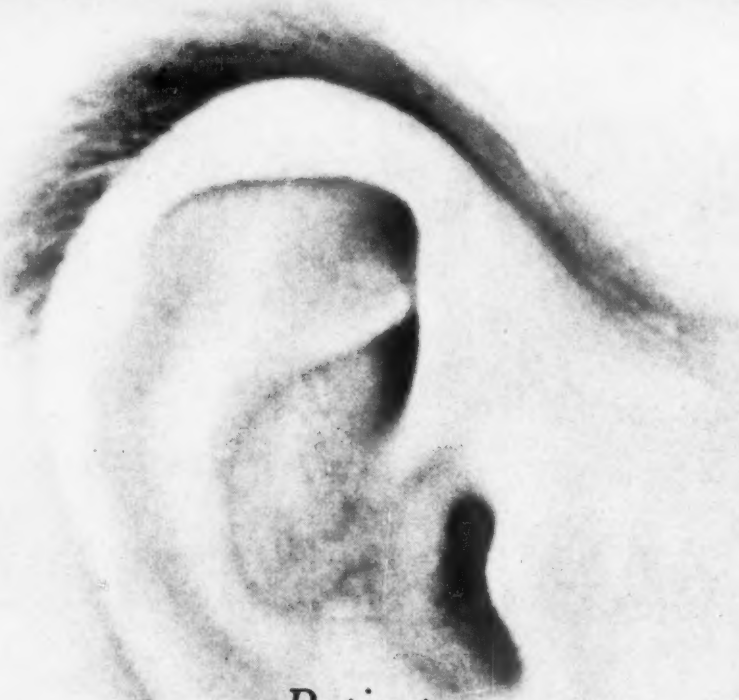

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Meeting
May 5, 1959

Some Aspects of Muscle Mechanics

By F. G. ST.CLAIR STRANGE, F.R.C.S.
Canterbury

ALTHOUGH we are taught that a muscle arises by a fleshy belly and is inserted by a tendon, yet phylogenetic considerations remind us that originally all limb muscles acted proximally, and indeed the muscles of the lower limbs continue, as a rule, to act proximally from their primordial point of fixation, the ground.

Two muscles will be considered and an attempt made to re-orientate some of our ideas and to explain certain phenomena which we observe, but may not always properly understand.

The Gluteus Medius

For the purposes of this paper, the term "gluteus medius" is used to signify the synergium of true abductors of the hip, rather than an individual muscle.

The gluteus medius is normally described as an abductor of the hip, i.e. an abductor of the femur on the pelvis. In everyday life this is a rare activity and one not normally undertaken against any significant resistance. The real function of gluteus medius is abduction of the mobile pelvis on the fixed femur and the prevention of adduction of the pelvis on the weight-bearing hip under the superincumbent body weight. Fig. 1 represents a man walking during the weight-bearing phase of the right leg. The centre of gravity (ACW) passes, with each step, slightly to the weight-bearing side. In the diagram, the clockwise moment is W × PC and must be counteracted by an anticlockwise moment Y × PX. The abductors must therefore hold the point X down towards their true origin (anatomical insertion) at Q, the great trochanter, with sufficient force in the line AXQ, their average line of pull, to produce a horizontal force at X of 168 lb. weight. Their pull, therefore, must amount to no less than 336 lb. weight and is required at every step to prevent the pelvis falling into adduction, the so-called Trendelenburg gait. The reason for its being twice the body weight is because the average line of action of the glutei (at B) is only half the perpendicular distance from the pivot (P) to the centre of gravity at C. Inman (1947) calculates the figure at 2·4 to 2·6 times the body weight.

Two important observations emerge: firstly, the great magnitude of the forces which are involved. At every step the hip-joint has to withstand a thrust of nearly a quarter of a ton. Secondly, the resultant thrust is not, as is so often assumed, falling vertically upon the top of the head of the femur, but at an angle of some 20 degrees outwards down the neck.

After any leg injury the patient tends to reduce the moment of his body weight about the hip by moving his centre of gravity laterally. If he goes so far as to bring it vertically over the hip, all demand upon the gluteus medius ceases and we are left with the body weight only, *now* falling vertically, over the top of the head of the femur. This is the gluteus medius limp, or so-called "antalgic gait". This latter is a bad name, for the gait is not only called for in painful hips. Indeed, it is only necessary in gluteus medius weakness. If a Greek name is required, it should be called the "anti-asthenic gait".

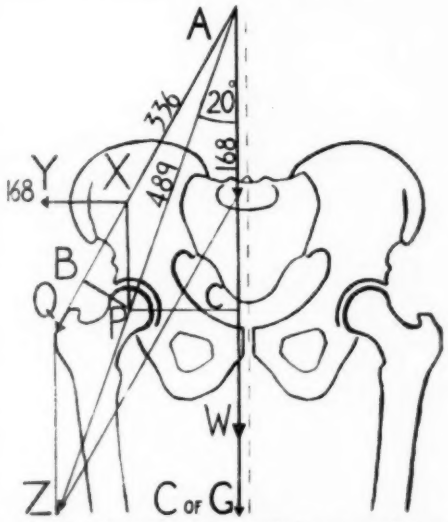


FIG. 1.—The body weight (W), less the weight of the right leg, is taken as 12 stone (168 lb.). AXQ is the average line of pull of the "gluteus medius"; APZ is the resultant and shows the direction and magnitude of the thrust in the hip.

From this appreciation of gluteus medius function, I think we may learn that no amount of leg abduction exercises alone will adequately retrain weak glutei. The essential activities are re-education in trunk carriage, in pelvic posture and in walking itself.

Again, the conception of the body weight falling, in a normal gait, on the top of the head of the femur is still widely held. This is wrong. The thrust is downwards and outwards in the line of the condensation of the trabeculæ at the calcar, of importance both when designing hip prostheses and when teaching patients to walk with them.

Thirdly, anything that weakens the gluteus medius, as in the lateral approaches to the hip, should be avoided: the Smith-Petersen approach, with subperiosteal reflection of the glutei, is far less damaging to them.

In McMurray's osteotomy, with displacement only, no change occurs in the mechanics of the hip, and with valgus angulation added, the stresses are actually increased (Fig. 2) unless the pelvis is tilted up and the spine curved to the same side, thus bringing the centre of gravity nearer the hip.

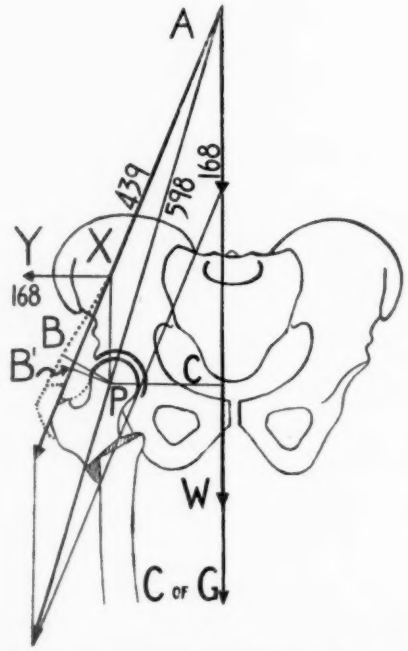


FIG. 2.—McMurray's osteotomy. Displacement and angulation. Forces increased owing to reduction of the distance BP to B'P.

In the adducted hip of osteoarthritis, and particularly if the strain is taken by the capsule rather than by the glutei (Fig. 3) the thrust in the joint rises enormously and may reach half a ton. It is not surprising that the cartilage wears out and that prostheses break. If patients are

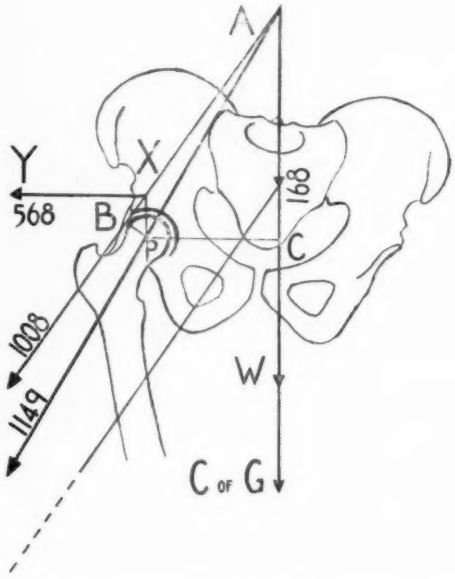


FIG. 3.—Osteoarthritic hip with adduction and strain taken on thickened capsule. Enormous increase of load in the hip.

allowed to walk on stemmed prostheses, either with an anti-asthenic gait or with an adducted hip, the stems will break or will work loose in the femur.

The Tibialis Anterior

The latest edition of Buchanan's Manual of Anatomy (1953) reads: "The tibialis anterior, acting on the free limb, produces extension of the ankle and inversion of the sole of the foot at the sub-taloid joint. When the foot is fixed on the ground, the muscle acts from its distal attachment. It now draws the leg forwards over the foot by movement at the ankle-joint, thus giving the body the thrust forward required in walking." Here, at least, is a recognition of the reversal of muscle action I have mentioned, but it is a very unsatisfactory description of its true function.

In walking, at the end of a step, the first part of the foot to strike the ground is the heel, at a

joint recently described by Rose (1958) as the "calcaneo-contact joint". In ordinary life it is, in fact, usually at the "shoe-heel contact joint" that this occurs (Fig. 4). In a man's shoe, the weight of the body is thrusting down some 3·2 in. (8 cm.) perpendicularly in front of this point. If the leg and foot were rigid, this would tend to "draw the leg forwards over the foot"

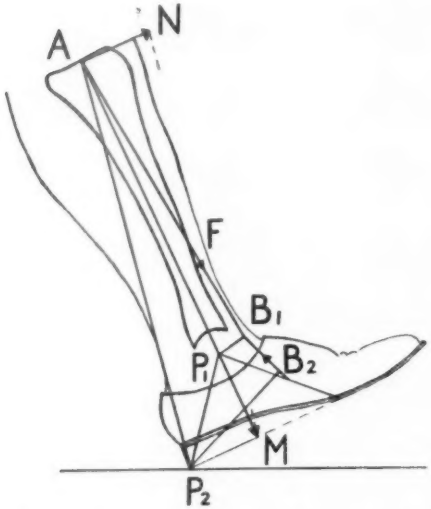


FIG. 4.—P_1 is centre of rotation of the ankle-joint. P_2 is the "shoe-heel contact joint" or pivot. AN is forward thrust resulting from action of M (kinetic energy coming down tibia) about P_2. (P_2M is about 3·2 in. (8 cm.) in many men's shoes.)

as Buchanan says, but not by "movement at the ankle joint", dorsiflexing, implicitly, the tibia on the fixed foot by the action of tibialis anterior. Tibialis anterior does, in fact, contract at this moment and almost makes the foot rigid and so imparts a forward jerk to the upper end of the tibia, transferring to it much of the kinetic energy coming down it. But it does so not by dorsiflexing the ankle but by preventing it from being forcibly plantar-flexed. By virtue of the perpendicular from the contact point to the line of tibialis anterior being about twice as long as that to the line of the tibial thrust, the muscle must produce a tension of about half the body weight at the moment of landing. Having caught the body thus, it now lengthens very slightly and, acting without a fixed point at either end, allows the angle of the ankle to open a little and lowers the fore-foot gently on to the ground fractionally before the tibia reaches the vertical. At this point it may help the tibia forwards towards the vertical, but it has only the purchase of the weight of the fore-foot, an almost negligible factor in relation to the weight of the body.

Apart from preventing sudden opening of the ankle and the instantaneous slapping of the fore-foot on to the ground (such an obvious feature of the drop-foot gait) the muscle has to overact considerably to counter two results of its own action. First, its upward pull produces a downward thrust on the tibia, and secondly, the "bowstring" effect on the pulley of the anterior retinaculum has a tendency to open the ankle-joint. (The "bowstring" effect has always a reverse action on a joint from that of a tendon's normal one.)

Nearly 40% of its power is expended in overcoming these contrary factors so that, at each step, the tibialis anterior must exert a pull of about 145 lb. weight in a 12-st. man.

I should like to re-define the action of tibialis anterior. In addition to its already recognized activities, it is the catching of the body weight at each step and the transfer of the downward acting kinetic energy into a forward direction, acting as a brake on forced plantar-flexion and paying out controlledly under very great load.

From this dynamic conception of its function there are practical points to be gained, of which I can here enumerate but two.

In the field of tendon transplantation about the ankle, not only do the muscles transferred for drop-foot require to regain a power of contraction we had not imagined, but also the cerebral cortical control of their action has to be completely relearned in more ways than one. They have become dorsiflexors instead of plantar-flexors, invertors instead of evertors, and their principal activity will be to act while lengthening instead of while shortening.

Again, in the restoration of ordinary function in a weakened tibialis anterior as, for instance, after immobilization or prolonged recumbency, a re-orientation of ideas may help. We might well abandon, I contend, attempts to make the foot dorsiflex against a resistance applied to the dorsum, an activity unknown in normal life, but aim instead at the far more satisfying effort of pushing a resistance away with the undersurface of the heel.

(NOTE.—Words such as stress, strain, force, &c., are used in this paper in their everyday sense, rather than in their strict engineering connotations.)

REFERENCES

BUCHANAN, A. M. (1953) Manual of Anatomy. 8th ed. Edited by F. Wood Jones. London; p. 607.
INMAN, V. T. (1947) *J. Bone Jt. Surg.*, **29**, 607.
ROSE, G. K. (1958) *J. Bone Jt. Surg.*, **40B**, 674.

The Natural History of Aneurysmal Bone Cyst

By L. W. Godfrey, F.R.C.S., and G. A. Gresham, M.D.
Cambridge

Aneurysmal bone cyst may be defined as a cystic lesion of bone containing clefts or spaces filled with blood which is in continuity with the general circulation. It often increases in size very rapidly and may expand the bone to an extreme degree. This expansion is frequently confined to one aspect of the bone.

The clinical and radiological appearances of the lesion closely resemble those of osteoclastoma, and the solid parts of it may appear similar histologically, so that it is sometimes classified as a "variant" of the giant cell tumours. Aneurysmal bone cyst, however, frequently commences in childhood when osteoclastoma is very rare.

The purpose of this paper is to present the microscopic appearance of the epiphysis related to a typical cyst. This shows clear evidence of infiltration by the cyst lining and suggests that the cells are neoplastic. The findings explain the frequent recurrence of the lesion after curettage and the occasional spread to adjacent bones. It seems likely that the cells of the cyst wall are of vascular origin and that the lesion is a form of hæmangioma, probably a hamartoma. Six other cysts are described which illustrate the probable natural history of the lesion, which is seen to resemble that of hæmangiomata in other tissues.

Aneurysmal bone cyst was first described as a clinical and pathological entity by Jaffe and Lichtenstein (1942). Several theories regarding the ætiology of the lesion have been proposed. Ewing (1940), Cruz and Coley (1956) and Lichtenstein (1957) all considered that the condition was caused by increased venous pressure, but Barnes (1956) suggested that it was an abnormal response to injury. Hadders and Otterdoom (1956), after a thorough pathological study, concluded that aneurysmal bone cyst was an angioma of bone. Parkes Weber (1956) also holds this view.

Case I.—A 3-year-old girl attended hospital in December 1956 with a swelling at the upper end of the left fibula: no history of injury or other causative factor. The swelling was slightly tender, but not red or hot.

Radiographically the upper end of the diaphysis of the fibula was distended by an apparently multilocular cyst (Fig. 1). The epiphyseal line and bony epiphysis were poorly defined, but apparently separated from the cyst by a plate of bone.

The whole upper end of the fibula, containing the cyst and epiphysis, was excised. Functional recovery in the leg was complete.

Fig. 1 (*Case I*).—Radiograph showing the expanded upper end of the fibula, the irregular line of dense bone adjacent to the epiphyseal plate and the small, rarefied ossific centre of the epiphysis.

Pathology.—On section the cyst was seen to be unilocular, but the bony wall was roughened by low projecting ridges which had caused the radiological appearance of a multilocular cyst. The cyst cavity was filled with fluid blood except for one corner which contained a wedge of cellular tissue. Microscopically, the cyst wall was seen to contain many blood-filled spaces lined by endothelium and separated by cellular fibrous tissue, composed of numerous dark spindle-shaped cells and occasional groups of multinucleate giant cells, the picture typical of aneurysmal bone cyst.

The epiphysis.—Three full-width sections of the epiphysis and related cyst were examined. The cyst wall was seen to be closely opposed to the cartilage in many parts, especially near the perimeter of the plate, but in others they were separated by a zone of provisionally calcified cartilage up to 1 mm. in width.

At the edge of the epiphyseal plate the blood spaces and cells of the cyst wall infiltrated between the cartilage columns of the plate and the periosteum, probably along the course of epiphyseal blood vessels (Fig. 2). Where blood vessels penetrated the plate, the cyst extended along them to pass through the zone of cartilage-cell columns (Fig. 3), and at one point, not illustrated, it reached the bony epiphysis. This infiltration of the cyst tissue along blood vessels, and the presence of blood-filled spaces in the infiltrating tissue suggests that the cyst cells are of vascular origin. It also explains the invasion of the epiphysis which is frequently seen

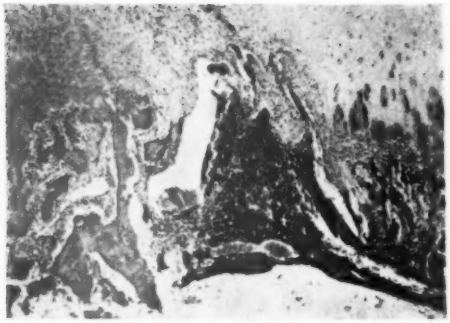


FIG. 2 (*Case 1*).—Photomicrograph of part of the perimeter of the epiphyseal plate where the cyst extends up to the cartilage-cell columns and infiltrates between the edge of the plate and the periosteum (× 28).

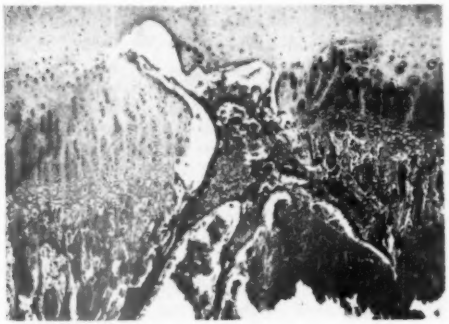


FIG. 3 (*Case 1*).—Photomicrograph of the epiphyseal plate where it is pierced by a blood-vessel. The cells of the cyst lining can be seen spreading along the channel toward the bony epiphysis (× 28).

radiologically in aneurysmal bone cysts, and the occasional spread to adjacent bones in the spine and tarsus described by Lichtenstein (1957).

The cartilage surrounding these penetrations was covered with a thin plate of woven bone. Where the invasion reached the bony epiphysis, it was apparent that this plate of bone was, in effect, a rigid tie across the plate, which would interfere with growth. The passage of blood vessels across the normal epiphyseal plate was studied by Ham (1953), who concluded that such penetration does occur and that the normal vessel walls must possess some special property to prevent ossification of the adjacent cartilage. Such a property is apparently not present in the vessels of the aneurysmal bone cyst.

In the central part of the epiphysis, where the cyst was separated from the plate, a curious change was noted (Fig. 4); the swollen cartilage cells were not arranged in columns but were

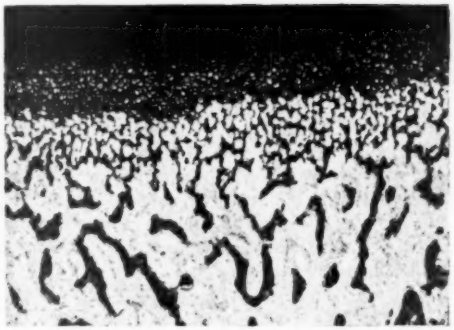


FIG. 4 (*Case 1*).—Photomicrograph of the central part of the plate where the cartilage-cell columns and provisionally calcified trabeculæ are irregular.

scattered irregularly, and the provisionally calcified cartilage was in irregular branching fragments, quite unlike the straight bars in the remainder of the metaphysis. The cause of this was obscure until the work of Gelbke (1951) was studied. He showed almost identical changes resulting from restriction of epiphyseal growth by wire bands. In this case a similar restriction could have been caused by the bone layers crossing the epiphyseal plate.

Discussion.—The study of this specimen suggests that the lesion was a neoplastic condition affecting the blood vessels. The radiographic and microscopic appearances are, however, very different from those of the hæmangiomata which are frequently found in the vertebræ and occasionally in other bones (Bucy and Capp, 1930). In these cases the radiographs of the flat bone and clavicle tumours showed a well-marked radial trabeculation, while the long-bone tumours produced a polycystic appearance. Microscopically the blood spaces retained their circular shape and the interstitial tissue resembled loose connective tissue with very few giant cells. The behaviour of hæmangiomata is, however, very variable. Winston Evans (1956) describes active invasion in some cases, mostly children, while others undergo thrombosis and fibrosis. The study of the other cases in this series shows that all these processes may occur in aneurysmal bone cyst and account for its variable natural history.

The Natural History

The onset of symptoms in aneurysmal bone cyst is frequently during childhood. Case 1 is the youngest example published so far, but all the cases described by Taylor (1956) and Barnes (1956) were under 21 years of age, as were 6 of 7

cases by Lichtenstein (1953) and 11 of 20 by Cruz and Coley (1956). In many of the other cases it is probable that the cysts had been present for many years before producing symptoms.

In most cases the lesion arises on the metaphyseal side of an epiphyseal plate, but the lesion may extend across the plate into the epiphysis at an early stage, and cysts presenting toward the end of growth frequently involve the epiphysis when first seen. This process is well illustrated by the next two case reports.

Case II.—A 12-year-old girl first noticed a swelling below her right knee one month before attending hospital in March 1957; radiographic examination revealed a smooth-walled cyst in the upper metaphysis of the tibia (Fig. 5). At exploration the cyst contained

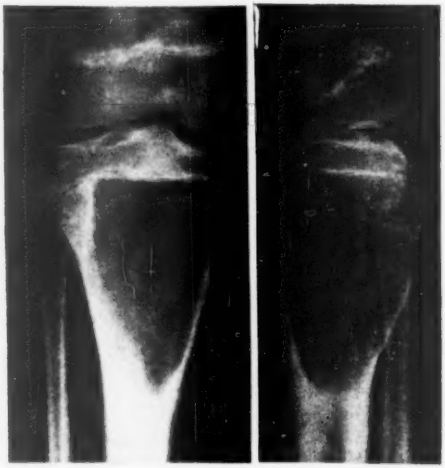


FIG. 5 (*Case II*).—March 1957. A unilocular cyst in the upper end of the tibia, slightly eccentric and producing marked thinning of the medial wall.

glairy fluid, and the soft-tissue lining, which was thick posteriorly, was removed by curettage. The epiphyseal cartilage was exposed in the wall of the cyst. Cancellous bone chips were packed into the cavity.

Three months after the operation radiographs showed the grafts apparently consolidating and the wall becoming thicker. After six months, however, the grafts had been absorbed and the cyst was obviously extending both laterally and upward through the epiphyseal plate (Fig. 6).

Treatment.—In view of the unsatisfactory response to curettage and grafting, further treatment was by radiotherapy alone. A dose of 1,500 r was delivered to the tumour, and the follow-up for the first year has shown a gradual recalcification and no further extension of the cyst.

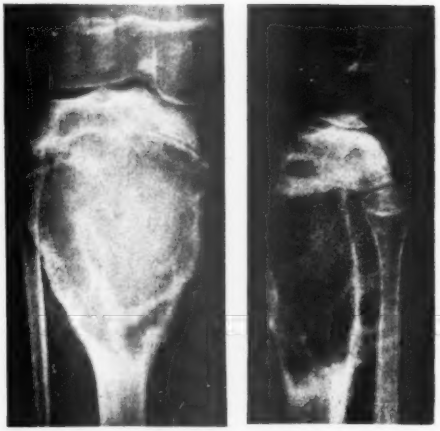


FIG. 6 (*Case II*).—September 1957. The cyst has enlarged and is extending into the epiphysis. The absence of bone from the antero-medial wall is shown.

Histology.—The curettings removed at the time of operation showed the typical endothelium-lined vascular spaces of aneurysmal bone cyst with a very cellular interstitial tissue containing many spindle-shaped cells and occasional giant cells, some of which contained pigment granules. The bone of the cyst wall was composed of newly formed woven bone.

Case III.—A 19-year-old girl attended hospital in 1951 with aching in the left ankle and swelling on the anterior surface of the lower end of the tibia for eight months; no injury or other causative factor. There was no limitation of ankle movement. The radiographic appearances are shown in Fig. 7.

Treatment.—This lesion was not recognized as an aneurysmal bone cyst. At biopsy the very thin cortex over the tumour with areas of hæmorrhagic discoloration under the periosteum suggested possible malignancy, so the whole of the lower end of the tibia was excised and the defect bridged by cortical

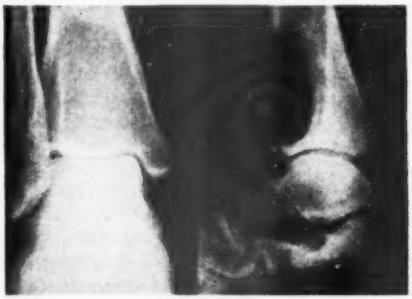


FIG. 7 (*Case III*).—Radiograph showing the cyst bulging forward from the lower end of the tibia and raising the periosteum from the adjacent normal shaft.

and cancellous bone grafts fusing the lower ends of the tibia and fibula to the talus.

The patient now has sound fusion of the ankle, a painless leg and no shortening.

Pathology.—The cyst was intersected in many places by thin grey to light brown membranes. The cyst wall consisted of delicate strands of connective tissue, covered by flattened endothelial cells. Giant cells in the wall of the cyst adjacent to lamellar bone were grouped around and often contained hæmosiderin. There was no histological evidence of resorption of bone. The appearance is very similar to that in Case I.

Another possible mode of onset has been described in the literature. Some cysts, pathologically indistinguishable from aneurysmal bone cyst, have been described arising from the midshaft region of long bones (Van Arsdale, 1893; Thompson, 1954; Jaffe, 1950; Lichtenstein, 1950; Geschickter and Copeland, 1949). These frequently occur in adults and are often related to trauma. Most of the early cases were diagnosed as ossifying subperiosteal hæmatomata. The next case is an example of this type of cyst.

Case IV.—A 43-year-old housewife first noticed a painful swelling in her right upper arm in September 1958, but did not attend hospital until January 1959 when a minor injury caused a great increase in the pain. No previous trauma.

There was a hard swelling deep to the muscles on the outer side of the upper arm, tender to deep pressure, but with no limitation of shoulder or elbow movement (*see* radiograph, Fig. 8).

The serum calcium and alkaline phosphatase were normal.

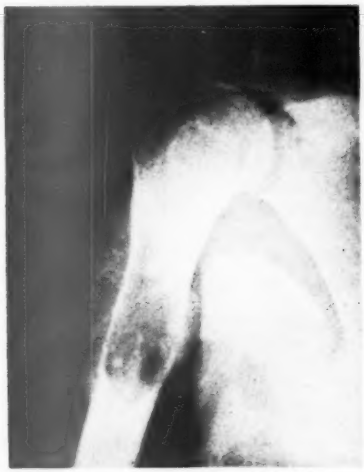


FIG. 8 (*Case IV*).—Radiograph of the right humerus showing a thin-walled cyst arising from the shaft of the bone.

A needle biopsy revealed sheets of fibroblasts with occasional giant cells and, in some parts, an endothelial covering.

The tumour was excised. It separated easily from an intact fibrous capsule over most of its extent, but was attached to the bone. It contained fluid blood and some grey tissue. The cyst lining was curetted from the bone, leaving a saucer-like defect on its antero-lateral aspect which was filled with bone chips. Recovery was uneventful.

Histological section of the cyst wall showed a typical aneurysmal bone cyst.

The subsequent progress of untreated cysts has not been fully elucidated in previous publications. That extension of the cyst may continue after skeletal growth stops is clear from cases in Lichtenstein's series, and several reported examples have reached a large size. It is probable, however, that some cysts remain undiagnosed throughout the life of the patient, having ceased to grow before they interfered with any vital structure. If these cysts are in fact hæmangiomata, thrombosis and fibrosis may be expected to occur in some. In a small cyst this may lead to complete resolution and recalcification; in a larger one some residual deformity would be inevitable. The next case probably illustrates an early stage in the resolution of a small cyst.

Case V.—A 40-year-old man attended for a routine chest radiograph in September 1956. This showed a

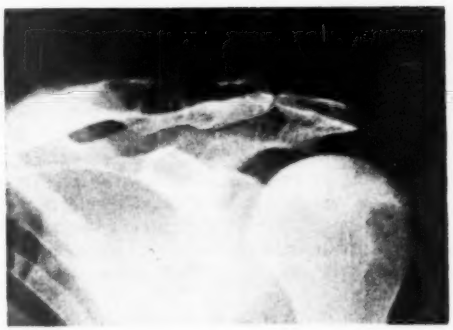


FIG. 9 (*Case V*).—Radiograph showing cystic distension of the outer end of the clavicle.

cystic condition in the outer end of the left clavicle (Fig. 9). He had no symptoms and there was no history of injury.

The cyst contained blood-stained serous fluid. The wall presented several projecting bony ridges and was curetted. Recovery was uneventful.

Histological examination showed the cyst lining to consist of delicate, almost myxomatous, connective tissue containing very few giant cells and covered with flattened endothelium. The lining was split by

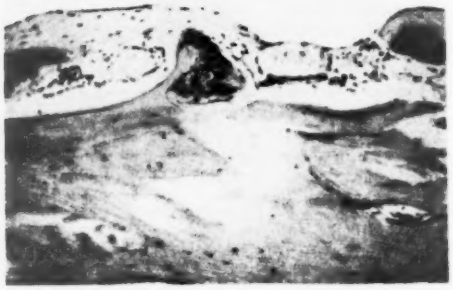


FIG. 10 (*Case V*).—Photomicrograph of the bony wall of the cyst showing the mature fibrous tissue containing blood-filled spaces and covered with endothelium (× 75).

several endothelium-lined clefts containing red blood corpuscles (Fig. 10).

Comment.—This cyst presented none of the active cellular tissue seen in the lining of the typical cyst, but the endothelium-lined cavity with blood-filled clefts in its walls retained the basic pattern of aneurysmal bone cyst.

The deformity left by thrombosis or fibrosis of large cysts has not previously been described and there are no established criteria for the diagnosis of such a lesion when found at necropsy.

Two cases were described, in each unconnected with the cause of death. A large cyst involving the petrous temporal and middle fossa was found in a woman of 72, and another in the left ilium of a woman of 75. These two cases presented a recognizable lesion characterized by a fibrous wall with plaques of calcification, surrounding an endothelial-lined cavity containing thrombus, the whole arising from a bone, usually near the site of a cartilaginous growth plate. Aneurysmal bone cyst appears, at present, to be the most likely cause of these lesions.

Treatment.—On the basis of this natural history, a rational basis for treatment can be formulated. In the growing child the cyst wall will probably be infiltrating the epiphyseal plate at the time the diagnosis is made, so that curettage, or local excision which does not remove the epiphyseal cartilage, is likely to be followed by recurrence. The ideal treatment is therefore complete excision of the cyst and the related epiphysis when this can be done without loss of function, as in Case I. When this is not feasible, radiotherapy is indicated, and is usually effective in small doses from which there is very little risk of post-irradiation sarcoma.

In adults, cysts in accessible sites can be cured by curettage or local excision, and this is the treatment of choice. Radiotherapy is only indicated when an inaccessible tumour is pressing on vital structures, such as the spinal cord, or is increasing in size.

Ætiology.—This is still uncertain. While this study suggests a neoplastic process affecting vascular tissue, it is apparent that aneurysmal bone cyst bears very little resemblance to the established cases of cavernous hæmangioma of bone. Some parts of the cyst lining, however, do resemble closely the cellular lining of the large cavities in certain hæmangiomata of the soft tissues. These tumours are in fact so variable in their structure that different types of presentation would be expected.

Summary.—The epiphysis related to an aneurysmal bone cyst showed active infiltration of the epiphyseal cartilage by the cyst wall, reaching through to the bony epiphysis. The appearances suggest that the lesion is a form of hæmangioma.

The natural history may be summarized thus:

Onset, usually in childhood, as a proliferation of vascular tissue in the bone adjacent to a cartilaginous growth plate or, in some cases, in a subperiosteal hæmatoma.

Growth by: (1) Active invasion, mainly along blood vessels causing early transgression of the epiphyseal plate. (2) Passive distension of the vascular spaces in the tumour by the pressure of the contained blood.

Inactivation by fibrosis or thrombosis leading to: (1) Absorption and recalcification of small cysts. (2) The formation of a chronic, thrombus-filled cavity surrounded by endothelium, fibrous tissue and bone in the site of a large cyst.

Acknowledgments.—We wish to thank Dr. A. M. Barrett, Mr. R. W. Butler, Mr. T. J. Fairbank and Prof. J. S. Mitchell for permission to publish the cases and for invaluable assistance in the preparation of this paper: also Mr. D. J. Martin for details of Case II and Mr. A. B. King for access to Case IV. The photographs were prepared by Mr. S. W. Vince and Mr. S. W. Patman to whom we are very grateful.

REFERENCES

BARNES, R. (1956) *J. Bone Jt. Surg.*, **38B**, 301.
BUCY, P. C., and CAPP, C. S. (1930) *Amer. J. Roentgenol.*, **23**, 1.
CRUZ, M., and COLEY, B. L. (1956) *Surg. Gynec Obstet.*, **103**, 67.
EVANS, R. W. (1956) Histological Appearances of Tumours. Edinburgh.
EWING, J. (1940) Neoplastic Diseases. A Treatise on Tumours. 4th ed. Philadelphia.
GELBKE, H. (1951) *J. Bone Jt. Surg.*, **33A**, 947.
GESCHICKTER, C. F., and COPELAND, M. M. (1949) Tumours of Bone. 3rd ed. Philadelphia; p. 309.

HADDERS, H. N., and OTTERDOOM, H. J. (1956) *J. Path. Bact.*, **71**, 193.
HAM, A. W. (1953) Histology. Philadelphia; p. 237.
JAFFE, H. L. (1950) *Bull. Hosp. Jt. Dis.*, **11**, 3.
——, and LICHTENSTEIN, L. (1942) *Arch. Surg., Chicago*, **44**, 1004.
LICHTENSTEIN, L. (1950) *Cancer*, **3**, 279.
LICHTENSTEIN, L. (1953) *Cancer*, **6**, 1228.
—— (1957) *J. Bone Jt. Surg.*, **39A**, 873.
TAYLOR, F. W. (1956) *J. Bone Jt. Surg.*, **38B**, 293.
THOMPSON, P. C. (1954) *J. Bone Jt. Surg.*, **36A**, 281
VAN ARSDALE, W. W. (1893) *Ann. Surg.*, **18**, 8.
WEBER, F. P. (1956) Interesting Cases and Pathological Considerations. London; p. 23.

The Management of Fractures of the Tibial Spine in Children

By JOHN SHARRARD, M.D., F.R.C.S.
Sheffield

THE object of this paper is to define the place of conservative and operative treatment for fractures of the tibial spine in children. It is based on experience of 10 patients, 5 treated conservatively, 4 operatively and 1 untreated until he was first seen four years after injury.

Clinical features.—The children's ages ranged from 4 to 14 years. They had suffered either a rotational strain at the knee, or, more commonly, a blow applied to the front of the thigh with the knee flexed, as by the handle of a wheeled toy that had tipped back. The clinical findings were characteristic—a flexed, painful knee, signs of hæmarthrosis and possibly a bruise or abrasion on the front of the thigh. A lateral radiograph of the knee showed a flake of bone raised from the tibial plateau, not easily visible on antero-posterior films (Fig. 1).

Pathology.—The injury was always much more extensive than the radiographic evidence suggested. With the flake of bone, a large area of surrounding articular cartilage of the upper surface of the tibia had been separated and displaced upwards and backwards by the anterior cruciate ligament (Fig. 2). The fragment, unlike that in adult fractures, was always attached posteriorly by a hinge of articular cartilage. In 3 out of 5 knees that were explored, the area of cartilage detached from the medial articular surface of the tibia was greater than from the lateral surface, and extended beneath the medial meniscus almost to the anterior or medial margins of the bone. The edges of the fragment were entangled with the medial meniscus, so that, when attempts were made to reduce it, the fragment "locked" over the upper surface of the meniscus. It was in these 3 patients that manipulation under anæsthesia before operation had revealed a block to the last 20 degrees of passive extension of the knee.

In one patient, in whom no such limitation was found, the fragment was smaller, did not involve much of the articular surface, and was

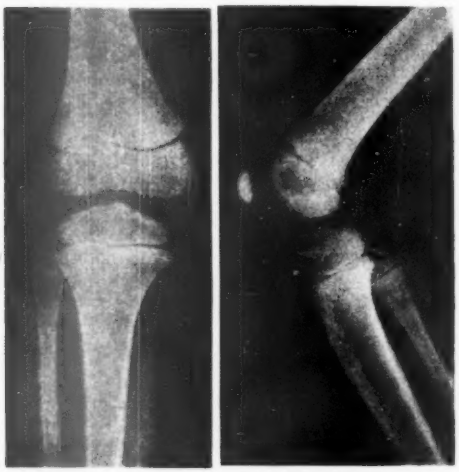


FIG. 1.—Fracture of the tibial spine in a child aged 8. The fragment did not reduce with simple extension of the knee, and there was some residual disability at follow-up examination.

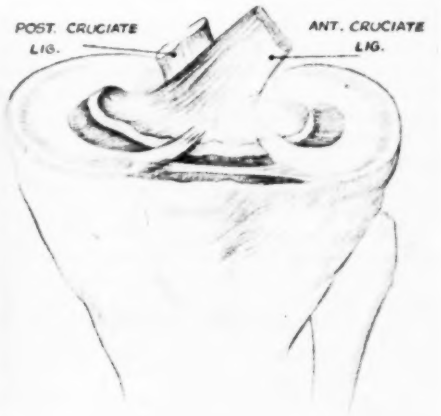


FIG. 2.—Diagram to illustrate the findings in fracture of the tibial spine. A large osteocartilaginous fragment is hinged posteriorly and is pulled upwards and backwards by the anterior cruciate ligament. Attempts to reduce the displacement may cause the fragment to lock on to the upper surface of one or other meniscus.

not displaced relative to the medial meniscus. In every case, the fragment was least displaced when the knee was slightly flexed; full extension, or flexion beyond 20 degrees, caused the anterior cruciate ligament to pull on the fragment.

Treatment and Results

Conservative treatment.—In all 5 cases the knee was aspirated if the effusion was tense, a Thomas' splint was applied for seven to ten days with the knee in slight flexion, followed by a groin to ankle plaster for about four weeks. General anæsthesia was only used when pain did not allow the knee to be extended. Maximum function was regained in every case not more than three weeks after removal of the plaster.

Follow-up examinations were made after periods ranging between one and five years. Two patients, aged 8 and 12, in whom the fragment had not been significantly displaced, had no disability and no clinical abnormality in their knees. Two patients, aged 4 and 12, with about 20 degrees of angular displacement of the fragment in the initial radiograph, had no disability but showed moderate anterior cruciate laxity and residual displacement of the united bone. One patient, aged 8, in whom there had been 40 degrees of angular displacement of the fragment (Fig. 1) and a block to the last 20 degrees of extension of the knee under anæsthesia, but whose knee had not been explored, had an unstable knee five years later and could not run. There was marked anterior cruciate laxity. It is very likely that the osteocartilaginous fragment had locked over the meniscus in this case, and would have been improved by open reduction.

Operative treatment.—In all 4 cases the knee-joint was opened through an antero-medial oblique incision, the fragment was reduced and a silk or catgut suture passed up from the region of the tibial tuberosity was used to fix the fragment. Although the suture traversed the epiphyseal plate, no late ill-effects such as Blount (1955) suggests were observed. In two patients the fragment could not be reduced until the medial meniscus had been removed, and in a third the meniscus was removed because it had been torn by the injury. The fourth patient, in whom the detached fragment was not large enough to lock with the meniscus, would almost certainly have resolved well with conservative treatment, and in a much shorter time. Post-operatively the knee was immobilized in a Thomas' splint for ten days, followed by a groin to ankle plaster for five weeks. Maximum function was not regained until between three and five months after removal of the plaster.

At follow-up examination, all had no disability. Two patients, aged 9 and 14, had no clinical abnormality in the knee apart from the operation scar. One patient, aged 5, had mild anterior cruciate laxity, and another, aged 11, had no cruciate laxity but showed a few degrees of limitation of flexion of the knee.

The remaining patient, who was first seen four years after injury to his knee at the age of 9, proved at operation to have a large central fragment displaced almost vertically upwards but still hinged posteriorly. The fragment had overgrown, causing limitation of extension of the knee, and was removed.

Conclusions.—This investigation suggests that neither conservative nor operative treatment should be the rule in the management of tibial spine fractures in children. I agree with Watson-Jones (1957) that conservative treatment by manipulation into a position 10 or 20 degrees short of full extension gives a satisfactory result in a short time in cases where the fragment is not large, or much displaced or locked. Radiographic evidence of much displacement of the fragment, or the finding of a block to full extension of the knee under anæsthesia, indicates the need for operative treatment, in spite of the expectation that return to maximum function is likely to be prolonged.

REFERENCES

BLOUNT, W. P. (1955) Fractures in Children. Baltimore; p. 173.
WATSON-JONES, R. (1957) Fractures and Joint Injuries. 4th ed. Edinburgh; p. 759.

Experimental Work on Femoral Neck Fractures [*Abridged*]

By A. C. BINGOLD, M.B., F.R.C.S.

London

IN 1957 and 1958 the writer was granted facilities for carrying out experimental work on fractures of the neck of the femur in the Faculty of Engineering at King's College, London. An outline of the study and certain conclusions reached on the structure, the strength and the mechanism of fractures of the femoral neck is herewith presented.

Method of study.—39 elderly cadaveric femora were fractured. 35 were subjected to static or shock loading in an Avery 30-ton testing machine (Fig. 1), being held in suitable wooden clamps, and 4 in an Izod impact testing machine. The experimentally produced fractures were compared with those seen in a clinical series comprising 58 cases.

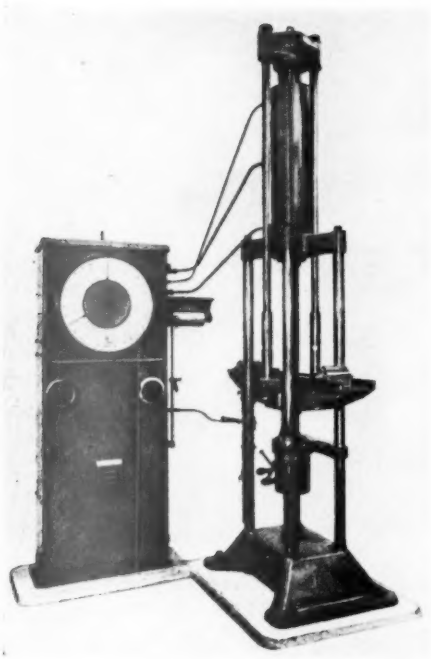


FIG. 1.—The 30-ton Avery testing machine used in the experiments.

Results.—When loads were applied to the head of the femur from above with the femoral neck either in the anatomical or horizontal position, fractures running from the superior cervico-capital junction to the lesser trochanter were produced in 15 out of the 19 specimens thus tested. In these 15 specimens the fracture line followed the outer border of the medial trabecular system. Only 4 specimens behaved differently. In two there were pre-existing sub-capital lines of weakness resulting in typical adduction fractures. In the other two the lateral trabecular system was particularly well developed at the cervico-capital junction and basal fractures occurred.

Loads applied to the great trochanter at right angles to the mechanical axis of the femur did not cause sub-capital fractures.

Loading the great trochanter in the line of the shaft of the femur and offering restraint to the femoral head was performed six times resulting in six sub-capital fractures of the abduction type.

An Izod testing machine was used to deliver blows by means of a weight attached to a pendulum to the inferior aspect of the femoral neck at the head-neck junction (Fig. 2). Typical abduction fractures resulted in the 4 specimens thus tested.

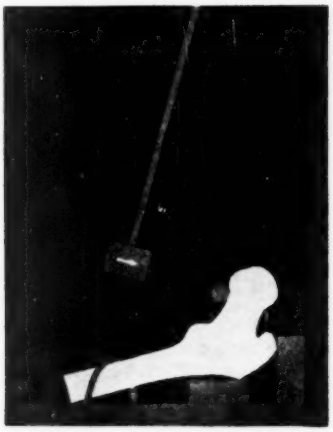


FIG. 2.—Schematic representation of the impact tests performed.

Loads were also applied to the inferior aspect of the femoral neck and restraint was offered to the superior aspect of the femoral head and to the femoral shaft. 6 specimens were tested. They all sustained typical adduction fractures.

Interpretation of Experimental Results

(1) The femoral neck is not homogeneous, but has points and lines of weakness. In most specimens tested by applying a bending moment to the superior or inferior aspects of the femoral neck, the fractures did not start where the bending moment was greatest, namely at the cervico-trochanteric junctions. The only possible explanation of this phenomenon is the existence of points of weakness. There were three such points: superiorly and inferiorly at the head-neck junction and at the lesser trochanter. In most specimens fractured by a load applied from above there was also a line of weakness skirting the medial trabecular system. Because the femoral neck is thus anisotropic it is futile to make plastic models, subject them to stress analysis by photo-elasticity and draw conclusions on the distribution of the principal stresses in a femoral neck.

(2) Male femoral necks are half as strong again as female femoral necks. The average bending moment withstood by 15 male femora was 0·357 ton in., by 16 female specimens of corresponding age 0·240 ton in.

(3) Fractures of the femoral neck are of two kinds: spontaneous and traumatic.

Spontaneous fractures occur in structurally weak femoral necks. As a result of fatigue failure or a sudden increase in the load on the femoral head by a sudden twist or trip, a fracture

starts at the superior cervico-capital point of weakness. This is painful and the muscles above the hip-joint go into spasm. The inferior cortex of the neck is fractured over the contracting psoas tendon, so that long before the patient falls to the ground her femoral neck is broken. Calculations were carried out from the measurements taken which showed quite clearly that the erstwhile owners of at least 7 specimens in the experimental series were in very real danger of sustaining spontaneous fractures. However, these fractures are rare. Only 2 examples were encountered in a clinical series of 58 cases.

Traumatic fractures are caused by a fall on the great trochanter. The kinetic energy of the falling body transmitted by the acetabulum decapitates the femur by direct violence.

If the femur is moderately adducted an abduction fracture results, if it is markedly adducted an adduction fracture results. In each case the fracture starts where the inferior lip of the acetabulum strikes the femoral neck (Fig. 3).

The majority of the fractures seen in the clinical series were caused by falls. Of 58 patients closely questioned, 34 gave a definite history of falls on their hips. There were six times as many adduction fractures as abduction fractures. Apparently most patients put out their hands to save themselves, thereby causing relative adduction of the femur by pelvic rotation.

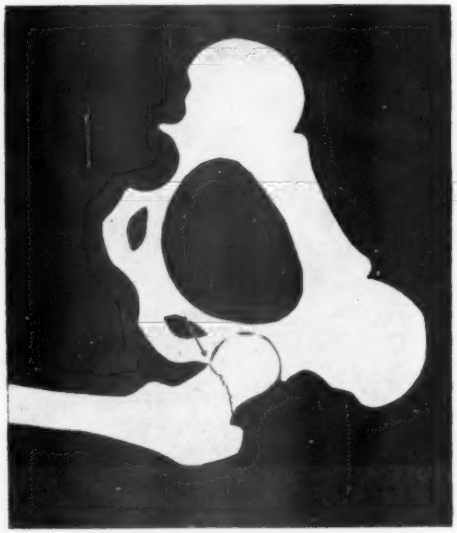


FIG. 3.—Mechanism of abduction fractures. If the inferior lip of the pelvis strikes the femoral neck lower down, adduction fractures are produced.

Acknowledgments.—It is a pleasure to record my thanks to Dr. J. M. Zarek, B.Sc., Ph.D., A.M.I.Mech.E. The illustrations were made by Mr. John Andrews.

Meeting
June 27, 1959

MEETING AT GUY'S HOSPITAL, LONDON

Prosthetic Replacement in the Primary Treatment of Fracture of Femoral Neck [*Abridged*]

By JOHN ADDISON, F.R.C.S.

Worthing

A SURVEY of cases of fracture of the neck of the femur treated by reduction and trifin nailing showed that good results were obtained in just under 50%. Table I gives results of 250 consecutive cases operated on by surgeons of the Worthing and Chichester Groups.

TABLE I.—RESULTS OF SMITH-PETERSEN NAILING—FRACTURES OF NECK OF FEMUR
(Average age 74)

	Died	Poor	Good
250 cases	49	80	121
	20%	32%	48%

An analysis of these cases into those under 75 years of age, and those of 75 and over is shown in Table II.

In the older age group the mortality (deaths from any cause during time in hospital) is naturally higher. The interesting features are the decrease in the percentage of poor results, and the fact that the percentage of good results remains very much the same. In the younger

TABLE II

	Cases	Died	Poor	Good
Total ..	250	20%	32%	48%
Under 75 ..	100	11	40	49
		11%	40%	49%
75 and over	150	38	40	72
		25%	27%	48%

patients, who are comparatively active, bony union was paralleled by good function. By contrast, in those of greater age, function, even with apparent bony union, was often markedly restricted.

Because of the low percentage of good results, an attempt to improve these by changing the method of treatment was made. As with bony

union of the fracture in younger or more active people function is excellent; it is essential to aim for this. The treatment of the under-75 group is not discussed in this paper—suffice it to say that in them there is no place for primary prosthetic replacement.

With the older patients the problem is different. In reviewing these cases it was felt that good results were mainly obtained in those where the fracture had initially been only slightly displaced, and presumably relatively stable, and with little soft-tissue disruption. In treating this older group, it was decided to continue reduction and pinning of such little-displaced fractures, and also those more displaced in persons who are active physically, despite advanced years. The remainder were the bad-risk patients—aged, in poor physical condition, frequently with concomitant disease, and with markedly displaced fractures. For them it was felt the use of a long-stemmed prosthetic replacement would have benefits. Previous experience with the short-stemmed Judet type of prosthesis had highlighted the main disadvantages of the procedure—fracture or wear of the prosthesis, and increasing instability with varus deformity. While being aware of other criticisms of this method of treatment—the use of a large metallic foreign body, possible wear of the acetabulum, and reaction of the soft tissues—we felt that these were lesser evils, slow to develop, and of decreasing importance in the older bad-risk patients. The anticipated end-result was not perfect function, but perhaps a quicker and more certain second best. Statistically this would be shown by a shifting of balance from poor to good. The vitallium Austin Moore self-locking type of prosthesis was chosen for use.

The operative procedure has been most adequately described by the originator (Moore, 1957). Two points merit emphasis. Every surgeon has his favourite approach to the hip, but the posterior route has the great advantage that when the leg lies naturally in external rotation after the operation the hip is stable, and this does away with the need for traction and allows early mobility of the patient. In this series there were no post-operative dislocations.

In making the incision it is much easier if it is made fairly high, from about the level of the posterior superior iliac spine, over the tip of the greater trochanter, and down this anteriorly; in this way the muscular insertion of gluteus maximus is avoided, and also the higher the incision the easier it is to get adequate retraction for the use of instruments in the femoral neck.

The second point concerns the seating of the prosthesis—it has to be done accurately. Here difficulty may be experienced because the upper part of the stem is rather broad. It is necessary to cut well back into the greater trochanter, and to clear thoroughly the bone from there and down the femoral shaft. If this is not done, and the rasp used too vigorously, it is pushed forward by the intact trochanteric bone, and a split is often made in or near the calcar. Another way of avoiding this is by use of a variation of the Austin Moore prosthesis which is made with a narrower stem. This is probably not quite as good, as the weight-bearing part of the prosthesis has been weakened.

The post-operative regime is easy and pleasant—naturally with some variations for differing circumstances. The present routine is: no traction, out of bed into a chair the day after operation, and weight-bearing commenced when the stitches are removed in twelve days. It is amazing how rapidly patients get a good pain-free range of movement in bed, though progress in walking is often slow and usually with some pain.

In aged people complications are unavoidable; minor wound sepsis has been present on several occasions, but cleared up quickly with good wound healing. Frank femoral thrombosis has occurred in only 2 cases.

The average stay in hospital has been six weeks, depending largely on the pressure on beds and the difficulty of disposing of many of these people.

The results of selected treatment are shown in Table III.

TABLE III

	Cases	Died	Poor	Good
Routine pinning (age 75 and over): Total	150	25%	27%	48%
Selected treatment (average age 79):				
Austin Moore prosthesis	53	16 (30%)	6 (11%)	31 (58%)
Pinning of good-risk and little-displaced fractures	17	2	2	13
Total	70	26%	11%	63%

Of the 75-plus group, from late 1957 to January 1959, there were 70 cases with an average age of 79. The Austin Moore prostheses were 53 in number—6 of these were over 90 years old. The mortality is slightly higher (30%), but these are selected worse-risk cases. The surviving patients were reviewed.

The "poor" cases had pain and restricted movements, for which it was usually impossible to find a cause; their function compared badly with their state before the fracture.

"Good" cases were those where their activities compared favourably with pre-accident status; most had some slight pain, though many had none. Practically all had virtually full move-

ments, but some weakness, and they walked with a stick. They were not normal hips, but their standard was better than in the unselected pinnings.

17 cases were selected as good-risk and little-displaced fractures, and treated by reduction and pinning.

The combined result of this experiment is that the mortality has not been changed, but on a short-term review the ratio of good to poor has a significant increase.

In bad-risk patients of over 75 with displaced femoral neck fractures prosthetic replacement would appear to be indicated.

REFERENCE

MOORE, A. T. (1957) *J. Bone Jt. Surg.*, **39A**, 811.

Congenital Dislocation of the Hip

By J. S. BATCHELOR, F.R.C.S.

London

I HAVE used the following routine of treatment since 1938. After gradual abduction of both legs to 90 degrees on a frame an attempt is made to reduce the dislocation by gentle internal rotation under general anæsthesia. If this is successful the legs are splinted in 90 degrees internal rotation and 40–50 degrees abduction by knee splints and a connecting bar (Fig. 1) or by a metal splint. When closed reduction fails open reduction is carried out forthwith.

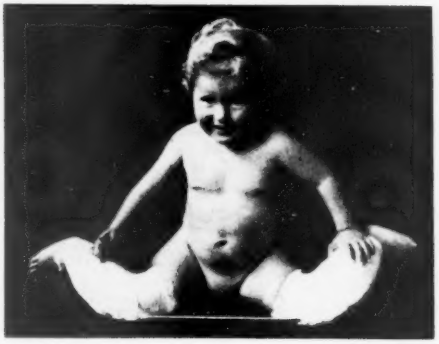


FIG. 1.

It is generally believed that splintage in internal rotation increases the anteversion of the femoral neck. This may be so when the legs are held in internal rotation and extension. The splintage allows, however, a free range of circumduction at the hips, and when the legs are flexed the position of the femora is very similar to that of the first Lorenz position (Fig. 2). The child spends a large part of its period of splintage in this position.

Anteversion is frequently responsible for early or late subluxation after successful reduction followed by splintage either in internal rotation or in the Lorenz position (Fig. 3). When subluxation occurs after splintage in the Lorenz position the influence of anteversion may not be appreciated. Effective correction of the anteversion is only possible when full internal rotation can be achieved.

A rotation osteotomy increases the stability of the reduction when it produces a coxa vara in addition to correcting the anteversion (Fig. 4).

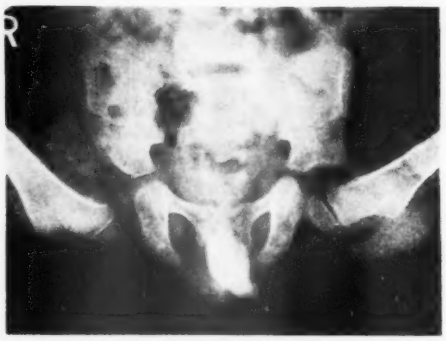


FIG. 2.—Dislocation right hip showing position with the legs flexed. The right femoral head appears low, but the result was very satisfactory.

Provided the osteotomy is performed under the age of 3 the varus is quickly corrected (Fig. 5).

Failure following rotation osteotomy may be due to tardiness or technical faults. When performed over the age of 3 the acetabulum may fail to deepen, and subluxation may recur. The leg must be placed in full internal rotation for one or two weeks before the osteotomy, for if this is not done the external rotation forces acting on the femoral neck may reproduce the anteversion, even when internal fixation is used.

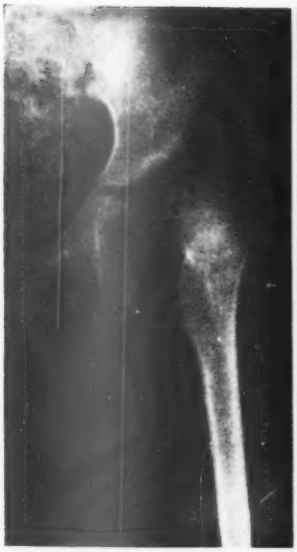


FIG. 3.—Subluxation due to anteversion following eighteen months in the Lorenz position, 12.8.41.

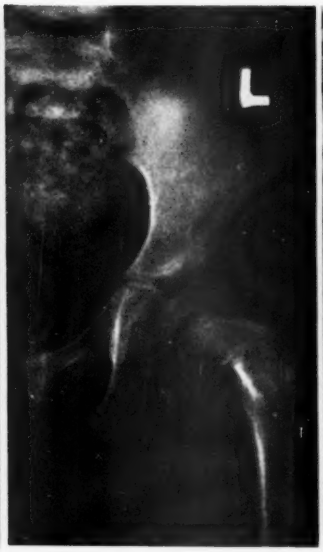


FIG. 4.—Varus position after osteotomy, 29.1.42.

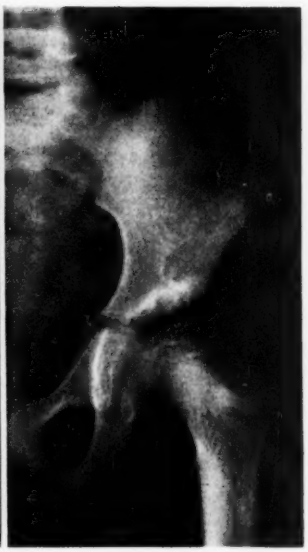


FIG. 5.—Correction of the varus two years later, 9.5.44.

The Treatment of Bilateral Osteoarthritis of the Hips

By P. A. RING, F.R.C.S.

London

PATIENTS who require treatment for an osteoarthritic hip fall into one of two groups. In the first the disease is confined to one joint, and the other hip is clinically and radiologically normal. In the second group both hips are affected, although only one may give rise to symptoms. There is rarely any difficulty in treating patients with unilateral arthritis, and good results can be obtained by a number of different procedures. On the other hand, success in a patient with bilateral arthritis of the hip is uncommon.

Since 1945 more than 300 patients have been subjected to major hip surgery at Guy's Hospital. Some of the patients who were initially regarded as suffering from arthritis of a single hip subsequently complained of pain in the other, but we were unable to find a single case in which a degenerative arthritis developed in a hip which was clinically and radiologically normal at the first examination. This does not necessarily indicate a fundamental difference between the pathology of these two groups, but it is an important clinical distinction which should be made at an early stage.

In assessing the different types of operations which have been performed in this unit one is particularly impressed by the frequency of hip arthrodesis. We have been very satisfied with the clinical results in these patients, although the rate of fusion leaves room for improvement, and fracture of the femur at the point of insertion of the nail is depressingly common. From time to time we have followed the orthopædic fashions, at first with the Smith-Petersen cup, later the Judet arthroplasty, and after this, the Crawford Adams cup. More recently, perhaps belatedly, the McMurray osteotomy has found favour. Pseudarthrosis of the hip, with or without osteotomy, has tended to be reserved for the exceptional case. The type of arthroplasty which has been performed has been dictated mainly by the year in which the patient presented for treatment, but throughout the whole period there was a tendency to treat the more severely affected hips by arthrodesis.

In the patient with bilateral arthritis there are three possibilities: (1) The second hip is only slightly affected, and never gives rise to any serious trouble; (2) the second hip deteriorates,

and requires surgical treatment; (3) both hips require treatment on the first admission.

In an attempt to discover whether the surgical treatment of one hip influenced the progress of disease in the other, we have reviewed the status of the second hip on a radiological and clinical basis. As might be expected, in almost all these patients, regardless of their initial treatment, degenerative changes in the second hip were progressive, and these changes were more pronounced on the clinical examination of the patient than on the radiographs. However, the rate of progress was not uniform. Some patients showed a rapid deterioration of the other hip; in others it was slight. We examined a number of factors to determine the cause of a rapid deterioration. The effectiveness of fusion in an arthrodesis clearly played no part, and neither did the position of fusion. Even if the arthrodesis failed to unite the other hip did not deteriorate excessively. Indeed, at review some of the most severely arthritic hips were seen in conjunction with a bony fusion on the other side in an excellent position.

In the patients with the various forms of arthroplasty the conclusions were very similar. There was a gentle deterioration of the other hip, regardless of the type of operation performed and, in general, regardless of its success. Occasionally, however, deterioration of the second hip was very rapid, and this may occur whether the arthroplasty has been successful or not.

We are left with the impression that it is the severity of the arthritis, and probably the nature of the arthritic process in the second hip, which determines its later deterioration. However, the treatment of the first hip may well determine whether or not the second requires operative correction. Severe arthritis in the remaining hip is compatible with good function in many patients with an arthrodesis. This, however, is also true of a good arthroplasty, and one certainly cannot argue that arthrodesis protects the second hip better than an arthroplasty. Indeed, if we simply compare the status of the hip opposite an arthrodesis with that opposite an arthroplasty, many years after the initial operation was done, we can see that these procedures are both of equal value. However, a satisfactory arthrodesis is usually more easily achieved.

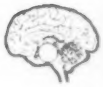
In those patients who first present with a bilateral arthritis in which both hips require surgical treatment, we have in the past attempted to retain mobility in both hips. The possible permutations and combinations of operations are endless, and the results have been most disappointing. Only 6 out of 30 patients admit that they have been improved by their operations; they all use 2 sticks for walking; most of them still have pain in one or both hips, and the range of movement is often small. These results have been so depressing that we have now adopted the policy of arthrodesing the worse hip before considering surgery upon the other. With this approach one meets an occasional patient who manages to spare the other hip, so that surgical treatment is unnecessary. More commonly, however, the presence of fixed deformity on the other side, or a rapid diminution in the range of movement if the patient is immobilized, demands operative treatment.

It is generally agreed that a patient who has had one hip arthrodesed requires movement in the other, but we have one patient with a bilateral hip arthrodesis who preserved good function for many years, and brought up a family. As her age advanced she became more incapacitated, and eventually asked for one of the hips to be mobilized. If the problem is one of *regaining* movement we have had more success with a Batchelor type of pseudarthrosis than with any other measure, and it is our experience that the range of movement tends to increase rather than diminish as the years pass. We have occasionally performed a cup arthroplasty upon the second hip, but this operation is less certain in its results. If it fails to relieve the pain, a pseudarthrosis as a secondary procedure is a much less satisfactory operation. Occasionally one sees a free range of movement in the second hip, and in a patient of this type a McMurray osteotomy is usually the procedure of choice. It is rare to find patients with bilateral osteoarthritis with a free range of movement in both hips whose symptoms are severe enough to consider surgery, but in these patients a bilateral McMurray is probably worth while.

One of the major problems when both hips are treated surgically is the retention of a reasonable centre of gravity. Many of our operations have failed, not because the patient was not relieved of pain, but because the residual fixed deformity of the hip was such that the centre of gravity fell in front of the feet, and the trunk could only be supported by the use of two sticks.

In reviewing these patients one is impressed by the great difficulties in treating the patient with bilateral arthritis. Good results are rarely achieved in patients with two stiff hips, and mobility is rarely restored. These patients should clearly be advised to undergo surgical treatment before they reach the stage at which mobilizing operations become necessary.

Mr. T. T. STAMM showed a film on **Metatarsocuneiform Arthrodesis.**



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Section of Otology

President—TERENCE CAWTHORNE, F.R.C.S.

Meeting
May 1, 1959

SYMPOSIUM ON THE DEAF CHILD

Dr. Mary Sheridan (London):

Delay or Failure in the Development of Spoken Language

In considering normal acquisition of spoken language in early childhood and the factors which contribute to delay or failure in its development, it is necessary to define the terms language and speech, hearing and listening, memorization, recognition and recall. I purposely do not employ the term perception, since otologists and psychologists use it differently. As used in this paper, *language* is the symbolization of thought in speech, gesture or writing for the purpose of interpersonal communication. *Speech* is the use of systematized vocalizations to express verbal symbols or words. *Hearing* is the reception of sound by the ear and its transmission to the primary auditory area of the cortex. *Listening* is the act of paying attention to the sounds received with the object of interpreting their meaning. Hearing is present at birth. Listening is the result of a long process of learning during the first few years. The efficiency of this process depends upon the amount of auditory stimulus the child experiences, upon the emotional qualities that invest his experience since these strongly influence the child's motivation to learn, and upon his capacity to memorize his experience in some coded form in his brain. Speech *memorization* may be likened to the compiling of a card index reference system, or perhaps, in view of Penfield's recent work (Penfield, 1958), to a library of tape recordings, which gradually become so enormous and complicated that a further elaborate system of cross references is required. The ability to facilitate these cross references depends upon intelligence. Stored auditory memories are available for *recognition* (which is matching a newly arrived sound against a previously recorded one) and *recall* (which is summoning a sound to mind at will when it is needed). Just as it is easier to match a colour accurately when one has a pattern to compare it with, than to call the precise shade to mind without a pattern, matching a spoken word is easier than evoking that word at will, and it is interesting to note that the child's recognition of familiar words (walk, dinner, shoe, ball, doggie, &c.) precedes his ability to use those words purposefully.

The ear itself has reached an advanced stage of development at birth and the neonate's ability to hear sound can be demonstrated, but the subsequent development of listening, memorization, recognition and recall depends upon orderly maturation of the central nervous system, accompanied by the opportunity to store his memory in the relevant critical period or period of optimum sensitivity for auditory learning.

The child's spontaneous acquisition of what might be termed the biologically-determined skills of locomotion, manipulation, vision, hearing, speech and social adjustment, upon which the acquisition of all subsequent voluntarily acquired skills is based, depend upon a close interrelationship between maturation and learning, each being dependent upon the other.

The infant's world is very small and only gradually expands, but within his field of physical reach and sensory awareness he is driven to explore and gather new experiences with a single-minded power of concentration that is truly astonishing. The normal sequence of developmental milestones (I would prefer to call them stepping-stones) is the same for all children, but the rate of progress in attaining them differs for every individual child. Following moving objects with the eyes comes before grasping with the hands, sitting before locomotion, and all these before the use of speech. If for any reason the child is denied the opportunity to store his kinæsthetic, tactile, visual and auditory memories during the stage of neurological maturation which is most favourable to their stockpiling, he appears unable to acquire the relevant skill with the normal spontaneity and completeness, and since he is impelled to explore, experience and communicate in whatever way is open to him, he will tend to substitute inferior patterns of functioning and consolidate them through repetition. Ritchie Russell (1959) has recently admirably summed up the matter as follows:

"We do not all use our brains in the same way. The auditory and visual pathways are anatomically constant, but the organization and direction of what arrives and its associations must differ for every individual. It is clear, however, that the method first used in early childhood will probably persist through life, so that the early months of life are the most important for the planning of brain mechanisms. Further the neuronal patterns used to learn a word in early childhood will probably be the same as those used in old age."

The compelling impulse to acquire all the biologically-determined skills appears to reach its zenith in the first 2 or 3 years, tapering off by 5 or 6 years, by which time habits of functioning are very firmly fixed and exceedingly difficult to alter. This is in line with what we can deduce regarding the critical period of speech development. Young children under 4 years who have heard and begun to talk, and who become deafened by infection or injury, rapidly lose their still unconsolidated habits of speech, whereas those over 4 years usually retain reasonably good powers of articulation, although the tone quickly becomes flat and monotonous since the voice can no longer be monitored by auditory feedback. Similarly Kanner and Eisenberg (1955) have reported, in a follow-up study of 19 non-speaking autistic children who did not talk by 4–5 years, that 18 were still mute four to nineteen years later, although some had originally spoken and were known to have hearing.

Edith Whetnall (1956*a*, *b*, 1958) has repeatedly stressed the importance of providing hearing aids and auditory training in the treatment of young deaf children, so that whatever usable hearing they possess may be exploited to the utmost, and I believe her reasoning to be sound. This belief is based on many years' study of the development of normal children and of recent opportunities to observe children with other physical and mental handicaps, who have been treated according to corresponding developmental principles.

As Fry (1957) has pointed out, spoken language implies communication between two minds. The process involved is threefold, reception, interpretation and expression. It has frequently been said that reception is a sensory process, interpretation an intellectual process, and expression a motor process. But this is an over-simplification of a highly complex activity closely involving thought, emotion, vision, hearing, kinæsthetic and vibratory sensation, as well as appreciation of time and of space. Introspection indicates that there are several well-marked stages before what is heard is understood. The phonetic units of speech, like other sounds, possess attributes of pitch, intensity and duration, and under ordinary circumstances are heard in three-dimensional space. The ear itself has no power of selection but is obliged to receive a confused medley of speech sounds and background noise. It is for the mind to decide whether or not to make the effort to listen. The willing brain then sorts out the speech elements from the entering din, arranges them in orderly sequences of words and phrases, refers these to the memory register and finally, in the light of intellect and the warmth of emotion, interprets their meaning. Expression is the result of the mind's decision to reply. The willing brain then marshalls appropriate ideas, formulates them in language, assembles the relevant kinæsthetic memories and initiates the necessary motor impulse. The muscular activities involved possess qualities of space, intensity or forcefulness, and duration. Whether or not these psychological steps possess neurological equivalents, experience shows that this complicated series of events may be slowed down or completely blocked at any of the above stages, either as a result of inborn defect or acquired disability.

In the past, largely from study of cerebral damage in adults, neurologists have endeavoured to localize the precise regions of the cortex concerned with different types of aphasia. Cartography of this sort is less fashionable than it was, but in any case we do not know how far the deductions made from study of damaged adult brains may also be true of the immature and still plastic nervous system of the young child.

The normal development of auditory communication, to quote Fisch's apt term (Fisch, 1957), may be readily observed from 2 or 3 months of age, by which time the infant has become sufficiently accustomed to the usual background noises of his immediate environment to ignore them, but a new sound will cause him momentarily to cease whatever activity he is engaged in to give it his interested attention. Nearby meaningful sounds, such as human voices, spoons in cups and running bath-water, evoke obvious delighted response. From about 5 months he turns his head to locate visually the origin of a sound, he laughs aloud in play with his familiars, vocalizes tunefully in reply to their talk and babbles to himself when he is alone. By 10 or 12 months he shows by his behaviour that he knows his name and the meanings of a few words. His babble has become a complicated jabbering which has all the cadences of real speech. By 12–15 months he is beginning to use

recognizable words in appropriate context. By 2 years he is putting two or three words together to form little sentences and his jabber is merging into intelligible self-talk. He tends to echo the prominent words in sentences addressed to him, he can ask for what he wants at table and communicate his toilet needs.

By 3 years he can hold simple conversations. His speech still shows numerous phonetic substitutions and omissions, which follow definite patterns (Sheridan, 1945) and must reflect the progressive development of normal auditory discrimination. By 4 years his speech is completely intelligible, he has a large vocabulary. He is incessantly talking and asking questions. He still shows a few immature phonetic substitutions usually of the /r/l/w/y/ and the /p/s/f/th/ group, but these have usually cleared up by 5 years. Confusions of the /th/s/f/ group, i.e. the highest frequency sounds, are the last to sort themselves out and may persist to 6 or 7 years even in normal children and longer still in the mentally retarded.

The main causes of delay or failure in speech development are: Lack of opportunity to learn in the critical period, impaired hearing, mental backwardness, delayed maturation of the central nervous system, brain damage, psychogenic disturbance, motor dysfunction, lesions of the peripheral speech organs.

These categories are not mutually exclusive but overlap in considerable degree. It is only possible in this paper to deal briefly with the first 3 causes, but these are the most frequent. The others need to be borne in mind, however, as they crop up every now and then in every pædiatric department, E.N.T. clinic and child guidance unit. Many show a bewildering multiplicity of symptoms and a baffling inconsistency of response to standard tests of all sorts, so that it is often impossible to diagnose them categorically.

Delay of speech development due to *lack of opportunity to learn* in the critical period appears so obvious that for many years I failed to give it adequate consideration, until experience with children of neglectful mothers, and children in residential nurseries and mental deficiency hospitals, drove the lesson home. The infant literally learns to speak on his mother's knee, that is at high decibel level, in situations which are familiar and understandable. The mother's laryngeal tones and vocal cadences convey affection, security and encouragement. Her words are addressed directly to the child and are concerned with simple objects and happenings which affect him personally in the here and now. From constant repetition the child learns to relate the tones of his mother's voice and the words she speaks with the things she speaks about. Gradually he begins to comprehend that every object and activity has its own name and that the spoken word can be used to produce all sorts of interesting results. Unless the child is addressed personally in this way and at this distance and level of loudness, and, just as important, unless he is listened to, encouraged and applauded when he attempts to speak himself, he will not learn to use spoken language, even if he hears normally, because the speech sounds that do accidentally reach his ears, have no "foreground" significance for him and are automatically disregarded as part of the general background noise.

Impaired hearing, whether peripheral or cerebral, implies defective reception of the phonetic units of speech. Broadly considered, the frequencies below 1,200 cycles per second provide most of the carrying power, energy and emotional colour of speech (Fry, 1957) while those above 1,200 c.p.s. are concerned chiefly with intelligibility. The chief characteristic components of all the vowel sounds, except the long /ee/ as in "feet" and its shorter form /i/ as in "ship", which have important components in the upper frequency bands, are in the lower and middle frequencies, the sound /oo/ being the lowest in pitch. Some idea of how the vowel scale rises in pitch from /oo/ to /ee/ may be obtained by speaking aloud or recalling mentally the following sounds (long vowels and diphthongs) /oo/oh/aw/ah/eye/ay/ee/. The chief components of all the consonant sounds are in the middle and high frequencies. The principal components of the nasal sounds /m/n/ng/ border on the low frequencies. Those of the /r/l/w/y/ group of continuants are somewhat higher in the middle frequencies. The plosives /g/d/b/ and their voiceless equivalents /k/t/p/ are still higher in scale bordering on the upper frequencies, while the sibilants /ch/sh/zh/z/s/ and the fricatives /v/f/th/ voiced as in "then", and voiceless as in "thin", are the highest of all in pitch. The fundamental vowel pitch of a woman's voice is approximately one octave higher than a man's (i.e. in the region of 256 c.p.s.). The highest consonant components of both male and female voices are much the same.

The *decibel level* at which a vocal sound is delivered determines its loudness and carrying power. The vowels all possess higher decibel intensity than the consonants, the sound /aw/

possessing the strongest and the sound /ee/ the least. The sibilants and fricatives possess the lowest decibel intensity and, therefore, have weak carrying capacity. The weakest sound of all is the voiceless /th/. The difference in intensity level between /aw/ the strongest, and /th/ the weakest phonetic unit is approximately 30 decibels.

Thus interpretation of the simplest spoken phrase imposes upon the listening brain the necessity to attend instant by instant to a large number of complex sounds which swing rapidly over differences of some 8 octaves in pitch and 30 decibels in intensity, and finally to synthesize the sounds heard into a meaningful whole. For practical purposes one may assume that a quiet conversational voice at 3 ft. carries to the listening ear sound-intensities varying between peaks at 60 db and troughs at 30 db.

The child with impaired hearing over any part of the speech range will receive, and therefore memorize and recall, imperfect phonetic patterns. His own speech will be correspondingly distorted. In high-tone deafness the consonant frequencies are mainly affected, and the child may begin to vocalize and use vowel sounds at the usual age, so that his hearing disability may remain unsuspected although his speech continues to be completely unintelligible. These children run a real risk of being considered mentally defective (Minski, 1957; Sheridan, 1944).

The tunes of speech, the stressing of syllables in phrases, the timing of vowel sounds, and the crispness of consonant articulation, all add to the liveliness and intelligibility of speech.

The nature of stereophonic hearing is still very imperfectly understood, but the fact that vocal communication normally occurs in three-dimensional space has certainly an important bearing on the child's acquisition of speech. Time and time again, when trying out clinical tests of hearing with very young and mentally retarded children, I was brought up against the difficulty of maintaining continuous auditory rapport in space, although it was simple enough to demonstrate hearing for distant isolated sounds. The explanation eluded me until I remembered the classic paper by Rene Spitz (1946) on the smiling response, and his discovery that the young infant child who smiled happily at the sight of a human full face, however superficially unattractive, would immediately cease smiling and return to his toys as if he were alone when that face was turned in profile. I then realized that my difficulty arose because a moment came when in withdrawing from him I dropped out of the child's auditory-spatial world. Experience has taught me that for normal children the field of continual auditory awareness for everyday meaningful sounds gradually expands from about 1½ feet at 6 months up to 10 or 12 feet (i.e. average room size) by 2½ years.

The *mentally retarded* child may reach the stage of being able to crawl or toddle beyond the optimum reach of his mother's voice before his habits of purposeful listening have been fully established. His hearing and speech behaviour will then be those of a younger child and he will need much the same purposeful auditory training as the child with impaired hearing, i.e. at mother-distance, and over a prolonged period. It is even possible that the temporary use of a high-fidelity auditory training unit or a hearing aid may be advantageous.

The observed pattern of normal speech acquisition in early childhood and the causes of delay or failure in its development become more comprehensible when they are viewed in the light of the child's maturing capacity to listen, to memorize, and finally to master the spoken language of his environment. Lacking the ability to hear and to speak, the higher realms of thought are rarely attainable, earning capacity is limited, and interpersonal communication, upon which so much of human happiness depends, is severely restricted. Our responsibilities with regard to early ascertainment, full assessment, adequate treatment and ultimate prevention of the language disorders of childhood and particularly those resulting from impaired hearing, for which so much can now be done, are grave and inescapable.

REFERENCES

FISCH, L. (1957) *Arch. Dis. Childh.*, **32**, 163.

FRY, D. (1957) *J. Laryng.*, **71**, 7.

KANNER, L., and EISENBERG, L. (1955) In: Psychopathology of Childhood. Ed. G. Caplan. New York; p. 227.

MINSKI, L. (1957) *Med. Pr.*, **237**, 56.

PENFIELD, W. (1958) The excitable cortex in conscious man. 5th Sherrington Lecture. Liverpool.

RUSSELL, W. R. (1959) Brain, Memory, Learning. Oxford; p. 82.

SHERIDAN, M. D. (1944) *Brit. med. J.*, ii, 272.

—— (1945) *Brit. med. J.*, i, 707.

SPITZ, R. (1946) *Genet. Psychol. Monogr.*, **34**, 57.

WHETNALL, E. (1956*a*) *Proc. R. Soc. Med.*, **49**, 455.

—— (1956*b*) *J. Laryng.*, **70**, 11.

—— (1958) In: Recent Advances in Pædiatrics. Ed. D. Gairdner. London; p. 329.

——, and FRY, D. (1954) *Lancet*, i, 583.

Mr. J. Chalmers Ballantyne (London):

The Early Diagnosis of Congenital Deafness

It will be evident, from Dr. Sheridan's paper, that the most conspicuous effect of congenital deafness is its effect upon speech, and it follows that the child who is born deaf—or partially deaf—will usually draw our attention to his handicap by delay or defect in his speech. And since it is in the second year of life that speech normally develops, it is at this time that most of the severer cases of congenital deafness will, or should, be brought to our notice.

But it is not quite as simple as that, and there are in fact three main age groups at which the handicap is commonly recognized.

Generally it is true to say that the more profound a child's deafness is, the earlier is it likely to be recognized; and there are some children, fortunately not many, whose deafness is so profound that they show few or none of the normal reactions of the hearing child to the loud noises of everyday life. In these cases, the handicap will commonly be noticed at some time during the first year of life.

The second group, the largest, consists of those children who fail to develop speech in their second year. It will include, of course, all those children who are born profoundly deaf, but most of the children who come within this group are partially deaf, often severely so.

The third group, a smaller but by no means insignificant one, consists of those children who have enough hearing to develop speech at the usual age but who, by reason of a partial deafness—usually for high tones only—develop a speech which is defective from the start. Not uncommonly this defect of speech may be so slight that it is passed off as simple "baby talk", and its true nature may be recognized only when the child goes to school. These children with high-tone deafness may escape detection for many years, and they often have so much hearing that it is extremely difficult to persuade their parents that there is any deafness at all.

But whereas the parents—and, indeed, the doctor—may be easily misled by these difficult cases, it is equally true to say that *when a mother thinks her child is deaf, she is very rarely wrong.* We cannot, and must not, ignore the mother's witness (Ballantyne, 1958).

A careful history should always be the first step in our examination of the deaf child; and at this stage there are four points that emerge. Others will be added later. (1) The hearing should be examined in any infant who fails to respond to the normal loud sounds of everyday life, (2) the hearing should be examined in any child whose speech is delayed, (3) the hearing should be examined in any child whose speech is defective, (4) the hearing should be examined in every child whose mother suspects that he is deaf.

Functional Examination of Hearing in Children

(A) *Diagnostic Tests*

As otologists, our main concern is to arrive at as accurate an assessment as possible of the child's hearing loss.

(1) *Distraction techniques.*—In testing the small child, it is of the utmost importance that he should be able neither to see nor to feel the source of the testing sounds. He must therefore be "distracted" by an observer while the examiner produces the various testing sounds. But the distraction must be "light", for if he is distracted too much, he may become so engrossed in the game he is playing that he will not respond even to sounds which are well within his range of audibility. It is never easy to distract just enough—not too little, not too much—but it is pointless to begin any formal testing until that point has been reached.

The newborn baby usually responds to *loud* sounds with the so-called Moro (or "startle") reflex, so aptly described by Dr. Mary Sheridan (1955) as "a sort of jerky extension of the spine and limbs, followed by a quick bowing movement of the arms over the chest, usually accompanied by a cry". This general withdrawal response is common up to the age of about 6 months, but thereafter the child begins to localize sounds and he usually responds by a simple turning of the head and body towards their source.

Many types of testing sound can be used: drums, xylophone bars, pitch-pipes and musical boxes, to mention but a few. Such instruments should convey, as far as possible, the whole range of the speech frequencies, but no test is complete until we have tried to obtain some idea of the child's hearing for speech itself.

In very small children, it is of the greatest importance that the sounds we use should be purposeful sounds, such as the mother's voice or the clinking of a spoon in a cup. The much louder, but meaningless, sounds of a drum or a xylophone bar may be completely ignored.

FIG. 1A.

FIG. 1B.

FIG. 1C.

FIG. 1D.

FIG. 1E.

In the first year or so of life, we must content ourselves with impressions, but at least we should be able to say whether a child has much hearing, little hearing or no hearing. And as he grows, so it becomes possible to assess his hearing with more and more accuracy.

(2) *Conditioning techniques.*—From the age of about 2½ onwards, attempts can be made to "condition" a child to carry out some simple act every time he hears a sound. The principle of these conditioning techniques can best be illustrated by a series of action-shots taken during an actual test (Fig. 1).

The child is seated at a small table with a nest

of coloured beakers. Opposite him sits the observer (in this instance, a teacher of the deaf), and beside her the examiner. The child is encouraged to *look and listen* as a xylophone bar is struck; and after the observer has demonstrated the test by picking out several beakers—one each time the bar is struck (Fig. 1A)—she helps him to do the same himself (Fig. 1B), by holding his hand gently on the next beaker and helping him to lift one out each time he *sees and hears* the xylophone being struck. This is repeated as often as necessary until he appears to understand what is required of him. He is then allowed to continue the game himself, without any help from the observer (Fig. 1C). As soon as he has learnt this "look and listen" game, the examiner can go behind him and the observer will beckon him to listen (Fig. 1D). Every time he *hears* the sound (without seeing its source), he will now pick out another cup, and the examiner can go farther and farther away from him (Fig. 1E) until he finds the greatest distance at which the child responds to this particular testing sound. Thereafter, other testing sounds—such as pitch-pipes of different frequencies, or various elements of the sounds of speech—can be substituted for the more easily visible xylophone bars; and these conditioning tests can be repeated with a hearing aid.

In children between the ages of 3 and 4, it will often take several unhurried visits, perhaps of half an hour or more, before the conditioning response is fully established.

(3) *Audiometry in children.*—Audiometry in children should be performed in much the same way as the conditioning techniques just described, and it differs from them only in the child's introduction (sometimes a difficult one) to the headphones. It has the great advantage (over free-field methods) of testing each ear separately, with pure rather than complex tones, and of giving a threshold measurement. An experienced technician—one, that is to say, who has special experience in dealing with children—can be expected in most cases to produce a reliable threshold audiogram from the (mental) age of 3 or 3½ onwards. Unfortunately, such technicians are few and far between.

(4) *Voice and whisper tests.*—From the age of about 4 onwards, the average child can be tested with simple words. The test is made much simpler if the words are presented to the child in the form of pictures, and I believe that the best of these word tests is the "rhyming word-picture" test of Michael Reed, Educational Psychologist at the Audiology Unit in Gray's Inn Road. The child is presented with a series of pictures (Fig. 2), each row of which shows four rhyming words. Each of the four words in each row, therefore, has the same vowel sound, but the consonant sounds are varied and we can learn a great deal from the child's ability to hear and distinguish these various consonant sounds, particularly the faint high-pitched sounds of "f", "s", "th", and so on. And it can be said, for example, that the child who can discriminate the words "tree" and "three", in a whispered voice at 6 feet, is almost certain to have normal hearing, for the only difference between these two words is in the initial consonant, and the "th" sound (of "three") is the faintest and highest-pitched consonant sound in English speech.

FIG. 2.

(This test has now been in regular use for over ten years, and I was pleased to hear recently that it is likely to be published in the near future by the National Institute for the Deaf. Reed, 1959.)

(B) *Screening Tests*

The diagnosis of congenital deafness is still established far too late far too often, and one of the biggest problems still facing us is the difficulty

of finding these children early enough. It is to the credit of Dr. Berenice Humphreys, of Leicester, that she conceived the idea of "screening" the hearing of every child in her own city within the first few years of life. After putting her scheme to Lady Ewing, a number of her health visitors were trained in Manchester to carry out screening tests, and between June 1954 and May 1957 full screening tests were given to no fewer than 4,409 children under the age of 5. Of this large number, only 4 were found definitely to be deaf and, of these 4, there was a family history in no less than 3. That is to say, of the 4 established cases of deafness, there was only 1 who was not known to be "at risk".

Now, it seems to me that this is very little reward for an enormous expenditure of time and effort, and I have taught for some time—mainly to medical officers of the London County Council—that we should concentrate our efforts on those children who are known to be, for one reason or another, "at risk". Four groups have already been mentioned—those children who have shown none of the usual responses to the loud noises of everyday life; those whose speech is delayed; those whose speech is defective, and those whose parents suspect they are deaf. But to these we must add several others, and this demands a knowledge of the causes of congenital deafness, and of the commoner causes of deafness acquired in the first few years of life.

Although there is still a depressingly large group of children (almost a half of all cases of congenital deafness) in whom the cause remains obscure, we do know that genetic weakness accounts for nearly a third of them; that a variety of prenatal influences (notably maternal rubella) accounts for more than 1 in 10; and that certain perinatal influences (notably birth injury, anoxia and kernicterus—the last due either to prematurity or rhesus incompatibility) account for a further 1 in every 5.

If we regard these, together with the four other groups, as "vulnerable" children, we should be in a position to find most of the children "at risk".

Quite recently Dr. Irene Howarth, Chief Assistant County Medical Officer to the Lancashire County Council has done a very interesting series of tests in which the incidence of deafness in a group of "vulnerable" children was compared with its incidence in a group of controls. Her list of vulnerable children had been provided by Dr. Ian Taylor, of the Department of Education of the Deaf, in the University of Manchester. He distinguished nine groups: (1) Children with cerebral palsy, (2) children with a family history of deafness, (3) children who were premature, (4) children with a history of abnormality in the antenatal period, e.g. virus infections of the mother during pregnancy, (5) children with a history of perinatal abnormality, e.g. asphyxia, rhesus incompatibility, &c., (6) children who have had a severe illness, e.g. meningitis, or who have been treated with streptomycin for any illness, (7) children who are not speaking well by the age of 2, and children aged 2–5 with speech defects, (8) children with a history of otitis media or chronic upper respiratory infections, (9) children with congenital abnormalities other than any mentioned above.

(This is almost identical with the groups enumerated by Fisch, 1957.)

To these I would add a tenth: (10) Any child whose mother has suspected him to be deaf.

During the last three months of 1957, Dr. Howarth tested 662 vulnerable children and found the incidence of deafness to be no less than 9·06 per 1,000. During the same period, the incidence of deafness per 1,000 children in her control group was as small as 0·65—only 2 children in over 3,000 tested. Hence the incidence of deafness was roughly fourteen times greater in the vulnerable group than in the control group (Howarth, 1958).

Ideally, perhaps, we should examine all children. But surely these figures speak for themselves, and as a matter of practical politics, we would seem to be justified in concentrating our efforts on the vulnerable groups.

Dr. Sheridan has examined many thousands of children with normal hearing, and she has recently described (Sheridan, 1958) a beautifully standardized system of screening tests. It need hardly be said that their main purpose is to find deaf children as early as possible and we should aim at doing our first screening test (in vulnerable children) at some time in the first year of life. It is not suggested that this should be done as an isolated examination, but rather that it should be included in the general examination (by medical officers of the public health services) at about the time of the first birthday, when most children are extremely easy to test. Such tests as Dr. Sheridan and others have described should at least allow us to find, at this vital age, any child who is born profoundly deaf; but some of the lesser degrees of partial deafness will escape

through the relatively coarse mesh of this initial screen, and other children will acquire deafness after this age. It is therefore important that there should be at least one further screening test for vulnerable children, and the age of school entry would seem to be a suitable time. For this purpose, the "rhyming word-picture" test of Michael Reed—combined, if time permits, with some form or other of "sweep" audiometry—should be eminently suitable.

Any child who fails to pass these screening tests should, of course, be referred without delay to one of those special audiology clinics where alone the facilities exist for full diagnostic tests of hearing. There is a great need for more of these clinics. Medical students must be taught about the deaf child; general practitioners must be constantly reminded about him; and medical officers of the public health services must be encouraged to look for him.

The vital need for an early start in training has never been more widely recognised than it is to-day. But it can never be said too often that this, in its turn, depends upon early diagnosis. It is never too early to start. The deaf children are there. And it is up to us as otologists to find them—by the establishment of more audiology clinics; by undergraduate and post-graduate teaching; by a closer co-operation with all our colleagues who work in this field; and by our own organization of the essential services.

REFERENCES

BALLANTYNE, J. C. (1958) *Med. World, Lond.*, **89,** 118.
FISCH, L. (1957) *Arch. Dis. Childh.*, **32,** 230.
HOWARTH, I. E. (1958) *Med. Offr*, **100,** 307.
REED, M. (1959) Personal communication.
SHERIDAN, M. D. (1955) *Med. World, Lond.*, **82,** 146.
—— (1958) *Brit. med. J.*, ii, 999.

Mr. R. H. Hunt Williams (Reading):

Early Diagnosis of Deafness

Since January 1959 my colleague, Dr. Kevin Murphy, has been investigating the "at risk" population in Reading. After sifting through a considerable number of clinical notes from maternity units, domiciliary midwives, and health visitors, an "at risk" population of some 260 children under 2 years of age was found. Some 86 children under the age of 1 have so far been screened. 5 were suspected of deafness. Of these, 2 were cured by syringing the ears—both had had infantile eczema and the meati were plugged with desquamated epithelium and debris—after which the hearing was found to be normal. 2 were suspected of partial deafness—possibly unilateral—and are being further investigated, and 1 appears to have severe deafness. An "at risk" register is now being kept and cases are notified as they occur.

It would seem that the vulnerable group consists of about 1 in 10 of the total births, which would give in Reading about 170 cases per annum for screening, and that by enlisting the co-operation of the Medical Officer of Health to keep a current "at risk" register, the problem of finding deaf babies should be reduced to a minimum.

Smyth and Farrow (1958) described a method for determining fœtal distress by fœtal electrocardiography and fœtal phonocardiography. It occurred to us that it might be worth while using this apparatus for testing cochlear function in the fœtus. Professor W. C. W. Nixon of University College Hospital kindly put his team, and Dr. Smyth his apparatus, at the disposal of Dr. Murphy, who has now carried out some forty tests. These preliminary investigations look promising and we are going ahead checking these results on neonates. These investigations are in their very early stage at the moment and it would be premature to give more than an indication here that pure-tone audiometry on the fœtus is a possibility, and we hope later to give a more mature report on this work.

If it turns out to be reliable, then it should be useful not only as a diagnostic test but also helpful in giving us a clearer picture of the ætiology of pre- and post-natal deafness.

The bulk of our work comes from an increasing enthusiasm for school audiometric surveys. Adventitious deafness is still very common and arises from a variety of causes. The value of routine audiometry in schools lies in indicating minor degrees of conductive deafness. In Reading all children have routine audiometry on entry at the age of 5. Only one has been found to have a significant degree of perceptive deafness. He has a severe cut-out at 2,000 cycles per second with almost normal speech.

In the unfamiliar surroundings at school, where the child is constantly required to acquire new information by ear, a mild degree of deafness is more significant than is the same amount in an adult. It is much more common than is generally realized and fortunately the majority respond satisfactorily after removal of tonsils and adenoids.

The significance of what one might term the conductive deafness overlay in children with a perceptive deafness should not be forgotten.

Children with perceptive deafness suffer from the same upper respiratory infections that their hearing companions do, and elimination of the conductive factor may improve their hearing to some extent.

Intermittent deafness is another problem. The allergic child, or the child with recurrent tubal obstruction, who may present with a 30–40 decibel hearing loss, tends to get into difficulties at school and at home for inattention. It is often difficult to tell how frequently he has these attacks and the duration. The hearing may be improved dramatically by eustachian inflation but not always with lasting benefit. Some respond to adenoidectomy, irradiation of the nasopharynx, or the exhibition of antihistamines, and some of them do not. On occasions I have trained the parents to test the hearing. Recurrent otitis presents a similar educational problem. These children, in addition to losing schooling because of their medical problem, often get out of the habit of listening on account of intermittent deafness. They should be allowed to sit in front in class and some we have issued with hearing aids.

Prophylaxis.—We still see far too many chronic discharging ears and minor degrees of deafness in the second decade of life. 3% of National Servicemen are rejected on account of otitis media. In the areas where the school leavers were specially examined, the percentage with present, or evidence of past, infection was much higher than that found by the Medical Boards (*Health of the Schoolchild*, 1958). That these teenagers should have passed through the sulphonamide and antibiotic era is a matter which must give rise to serious thought. We spend a great deal of our time in the theatre attempting, with varying success, to salvage and restore hearing in ears which might, with careful prophylaxis, never have got into this chronic state, and I would suggest that there is scope here for research into preventive medicine.

REFERENCES

SMYTH, C. N., and FARROW, J. L. (1958) *Brit. med. J.*, ii, 1005.
Hlth. Sch. Child., Lond. (1958) p. 33.

Mr. P. S. Taylor (Reading):

How the Deaf Child Fits into the Educational System

Educational law recognizes ten kinds of handicap which require special educational treatment. Defective hearing may be among the most serious of these handicaps, as inability to communicate makes education almost impossible. A language is therefore essential. But language is best learnt at an early age and this learning is normally based on considerable previous experience of the hearing of sound symbols. If children do not learn the use of language at the optimum age, they have serious difficulty in catching up later, and, in fact, may never do so.

Normal schooling does not begin until the age of 5 years, but the Local Education Authority has a duty to ascertain which children are handicapped and may require a child to be medically examined for this purpose from the age of 2 years. There is no particular difficulty about the medical examination of children once they have started school, but this is too late for the discovery of deaf children. Though it may generally be true that the totally deaf child is discovered by the age of 2 or 3 years, I am frequently astonished by cases in which a child of 4 or 5 or even older has been thought to be dull mentally, to suffer only from a speech defect or to be maladjusted, when in fact the child has quite a serious hearing loss which has not been discovered and which is the basic cause of the other symptoms.

A solution, which is becoming commoner, is the use of Health Visitors who have been given some training in recognizing the signs which may indicate some hearing defect in a child. In Reading this is done. But we felt that there might still be some children who might be missed, and we had the idea of using also the School Attendance Officers. In Reading, and in some other areas, though not in all, the Attendance Officers keep a running census of all children of compulsory school age and under, based on visits paid annually to every house in the town. We need this not only to see that all children of school age attend school, but to help us in deciding where additional school places might be needed. We therefore arranged that both the Health Visitors and the School Attendance Officers should ask, informally, the following questions:

Major questions: (1) Is your child talking in sentences? (2) Can you understand everything he says?

Subsidiary questions: (1) Does he *always* understand what you say to him? (2) Does he *always* answer when called? (3) Has he a speech defect?

Final question: Do you think he has difficulty in hearing?

In the last eighteen months, as a result of some hundreds of visits, 71 children were referred for further tests by Health Visitors, Attendance Officers, or by Nursery School Teachers. Of these, 39 were found to have some hearing defect. The really interesting thing, however, is that only one of them had deafness of the perceptive type, and was given a hearing aid. All the others when referred to the Royal Berkshire Hospital were given treatment to which they have responded. Thus another important argument is revealed in favour of early ascertainment. Fewer children may grow up with impaired hearing.

I need hardly say that these procedures do not absolve the Authority from making every effort to discover any children with even a slight loss of hearing after they reach compulsory school age. Audiometric testing of all school entrants at the age of 5 years, and special tests for those thought to be educationally subnormal or maladjusted, those with speech defects and those suffering from cerebral palsy, are essential.

When the children whose education is likely to be affected by a hearing defect have been found, the Education Authority must then decide what special education is to be provided for them. This cannot be decided on the amount of hearing loss alone. As important are the child's intelligence, his experience of the reaction to him of others, the attention his mother has given him from an early age, and so on. The decision is not merely a medical one, and should be made, as in Reading, by a team consisting not only of the otologist and the school medical officer, but also by the teacher of the deaf and the education officer. An educational psychologist should also be concerned, if there is one available. In Reading, the teachers of the deaf attend the weekly clinics held by the otologist at the hospital. They also have joint sessions with the school medical officer before submitting a recommendation to me about a particular child.

Regulations under the Education Act distinguish between the deaf—pupils who have no hearing or those who have to be taught as if they had no naturally acquired speech, and the partially deaf—those with some naturally acquired speech but whose hearing is so defective that they cannot be taught in an ordinary school. These categories, decided in 1938, are probably now too simple. Increasingly, with the use of improved hearing aids, both group and individual, speech can be naturally acquired by children with quite a severe hearing loss. But there is no mention of decibels in these definitions. Until April 1, 1959, the regulations required that a deaf pupil had to be educated in a special school. Since then, although there is no regulation to that effect, the Minister assumes that authorities will normally regard education in a special school as being appropriate and that they will consult him if they propose to make alternative provision. There is thus a little more flexibility.

Of course, the question of school does not arise before the age of 2 years, but, if the handicap has been identified before that, much can be done in very many cases if the parents are given proper guidance, either in an audiology clinic or elsewhere. My own feeling is that though the help of everyone concerned must be enlisted—health visitors, psychologists, doctors—the specially trained teacher is the best person to give continuing guidance, and that the best place for it is in the home. I am also hoping to arrange for some guidance to be given in the friendly atmosphere of a nursery class, which I think has advantages over the clinic.

After a child reaches the age of 2, the question arises whether he should go to school or not, and, if so, to what kind of school. I think it is clear that any child with a significant hearing loss should be in the care of a trained teacher of the deaf as soon as possible, preferably at a school. In many cases this may only be possible if the child goes to a residential nursery school for the deaf, but in my view 2 or 3 is a very early age for a child to be taken from his mother, though there may be no alternative, especially if the child is totally or subtotally deaf. In some areas there may be a day nursery school for the deaf. In Reading we have established what is officially described as a partially deaf unit attached to an ordinary infant school with a nursery class which takes normal children from the age of 3. But I think this description is misleading. In fact what we have done is enlist the interest of the headmistress and staff of one of our best infant schools with a nursery class. We have acoustically treated one of the classrooms and equipped it both with a group and a loop hearing aid, and appointed a qualified teacher of the deaf to be responsible for the deaf children between the ages of 3 and 7 who are sent to that school. I must make it clear that no such child is totally deaf, though some are severely handicapped. Some of the children are in the special class for most of the week; others, as their speech becomes more fluent, hardly attend the class at all. All spend some part of the week with the hearing children in normal classes, have their meals with them, play with them. Each has his own programme in which the auditory training given,

either individually or in small groups, is based on his particular needs. Not more than eight children who require the attention of the specialist teacher for most of the day are admitted to the school at any one time. In addition there may be three or four others who spend most of their time in ordinary classes.

Apart from such provision of special educational treatment for children with significant hearing losses, there may be great advantage for some children whose handicap is not severe in attending an ordinary nursery school or class with a hearing aid, if appropriate. But I cannot emphasize too strongly that this is not sufficient for a child whose handicap is at all severe. In any case such children should be seen frequently by a qualified teacher of the deaf, in addition, of course, to any necessary medical supervision.

At 5 years of age a child is normally required by law to attend school full time. Again, similar choices may be open, depending on the availability of special day and boarding schools and of classes for the partially deaf in ordinary schools. Which choice should be adopted must again depend on a consideration of the needs of the whole child—his hearing loss, intelligence, temperament, &c.

In Reading we have a special class in a junior school which takes children from 7 to 11 or 12 years of age. This class was in fact started before the other, and quickly revealed the need for the class for younger children.

This is the class with which Mr. Ling has been working and he will give further details about it. It will be clear to you when you have heard him that he has been outstandingly successful in his work. I have often wondered, as have visitors to the class, how much of his success is due to his own personality, how much to his methods and how much to the fact that his pupils are mixing freely and frequently with hearing children in an ordinary school. I am quite clear that the teacher of such a class in an ordinary school must be above average in personality and quality as a teacher. Many responsibilities are placed on him which are not usually placed on the ordinary teacher in a school for the deaf. Because of his isolation from his colleagues, he must not only be accepted as a full member of the teaching staff of the school, supported by the Head, but must also be regarded as a specialist member of a team consisting of the school medical officer, the otologist and the education officer. All this is true in his case. I am also clear that his methods and techniques, though perhaps not the only methods and techniques appropriate for deaf children, would be largely successful in any teaching environment. It is evident by now that there has been great advantage to his pupils not only in improving their ability to communicate, but also in their social maturity, from the possibility they have of working, playing and making friends with hearing children in a large, well-organized junior school.

At the secondary school stage the problem becomes more difficult. At that age children's interests and abilities begin to differ more widely. They need a more differentiated curriculum, with a wider range of subjects. If the child is in an appropriately organized special school, qualified teachers of the deaf may be available to provide for these differing needs. So far, in Reading, we have only recently had to face the problem. The suggestion has been considered that we should start a third class for deaf children as part of an ordinary secondary school. I am reluctant to agree to this as it is difficult to find any one secondary school which can cater for the wide range of abilities and aptitudes of all the children. We have therefore decided, experimentally, that each child on leaving the junior school should be placed in any one of the various secondary schools in Reading where his needs can most appropriately be met. One child has this year been accepted for admission to the Mary Hare Grammar School for the Deaf. Some, last year, were able to join ordinary secondary schools in the town, with continuing, but occasional, supervision from the teacher of the deaf. Others will this year also be placed in ordinary secondary schools, though several of them will require to continue with regular auditory training which will be given by the teacher of the deaf with an individual training unit. Some of them will also need special tuition by an ordinary teacher who normally takes groups of backward pupils in the secondary schools. I can only say, at this stage, that what we are proposing is regarded experimentally and the progress made by the children will be watched carefully and the arrangements modified if it seems necessary.

Another responsibility of teachers of the deaf in Reading, as also in some other areas, is the supervision of those children whose hearing loss is slight enough for them to continue in ordinary schools without regular special educational treatment. Some may have spent a short period of, say, six months in one of the special classes, and have been returned to normal schools. In either case there is a danger that their hearing difficulties will lead to their being retarded educationally unless constant attention is paid to their progress, and unless their hearing aid, if they wear one, is kept in good order and they are watched to see that they use it.

Mr. Daniel Ling (Reading):

Some Results of Auditory Education in a Special Class for Children with Defective Hearing

The educational treatment of deafness has lately become a field full of controversy: but from the controversy is beginning to emerge a new and rapidly growing philosophy. This means change—change towards the prevention of handicap caused by deafness rather than the later alleviation of such handicap through remedial teaching.

It is now generally recognized that early and efficient training of most young deaf children can do much to prevent the personal, social and educational handicap frequently found in our older deaf people to-day. However, at the moment late detection and diagnosis and late or ineffective early treatment are still common features in a deaf child population. It is mainly with these less fortunate deaf children that I have had to deal and it is the results of their treatment I wish to present.

The handicap accompanying deafness stems mainly from impaired communication rather than from the deafness itself. It therefore seems logical to emphasize the acquisition of communication skills in a remedial teaching programme. In the Palmer Unit, a special class for hearing-defective children in Reading which is situated in an ordinary junior school, remedial training was primarily through the use of residual hearing. Group and individual mains amplifying equipment was available and each of the 8 children in the class was equipped with an individual transistor aid, which was worn every waking hour of each day. In brief, the work of the unit was to teach each child to live and learn as far as possible through hearing. Lip-reading, though encouraged in social situations, was suppressed during training largely by means of tape recorded lesson material. Figs. 2, 3, 4 and 5 and Table I illustrate the effectiveness of the training.

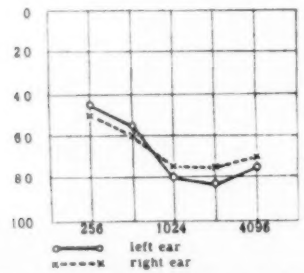

FIG. 1.—Pure tone audiogram of Case I on admission to the Palmer Unit at 6½ years of age, at which time there was no response to speech audiometry.

Case I (Figs. 1–3) is a child of Polish parents. Poor English in the home has retarded her speech development considerably, although she now speaks more clearly and grammatically than either her mother or father. Her growth of natural speech and language stems largely from her increasing ability to discriminate speech through hearing. Figs. 1–3 show that although this child's hearing for pure tones deteriorated, her hearing for speech improved.

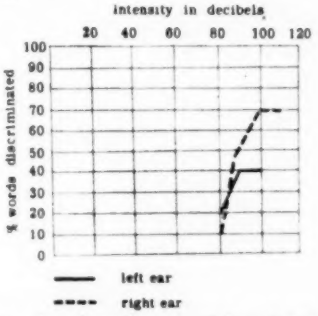

FIG. 2.—Speech audiogram of Case I taken three months after admission. No change had occurred in her pure tone audiogram.

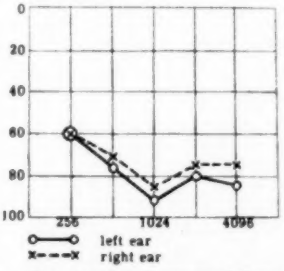

FIG. 3A.—Pure tone audiogram of Case I after two years' training.

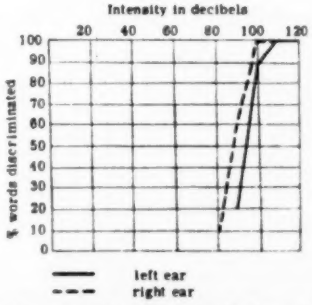

FIG. 3B.—Speech audiogram of Case I after two years' training.

Case II (Fig. 4) is a deafer child. Diagnosed at 4 years of age, she spent a year in an ordinary nursery class where, through the use of her hearing aid, she learnt her first words and phrases. From 5–7 years she attended a residential school for the deaf. On admission to the Palmer Unit at the age of 7 she was unable to discriminate between monosyllables having the same vowel sounds and her speech was unintelligible. As her ability to use hearing improved her speech took on a more natural quality. She is now easily understood on first hearing by anyone she meets.

Cases I and II were children who had spent most of their lives before treatment commenced in a hearing community and Case I had had no specialist help prior to admission.

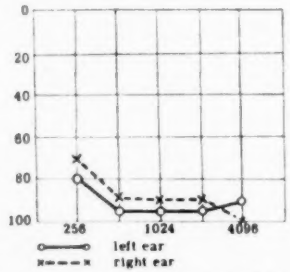

FIG. 4A.—Pure tone audiogram of Case II after three years' training.

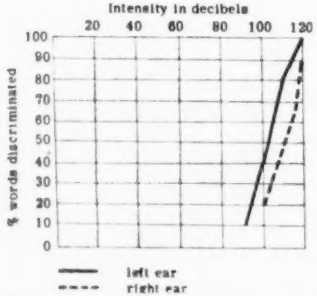

FIG. 4B.—Speech audiogram of Case II after three years' training.

Case III, however (Fig. 5), was admitted to the Palmer Unit after he had spent approximately six years in a residential special school for the deaf. This is, I think, an example of ineffective early treatment: ineffective, perhaps for a variety of reasons. On admission he had no intelligible speech and very little ability even to articulate simple sounds. Furthermore, he had no ability to discriminate between sounds of speech. However, this child made rapid advance in speech discrimination during six months' treatment in the Palmer Unit and

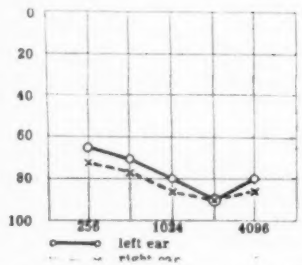

FIG. 5A.—Pure tone audiogram of Case III after six months' training.

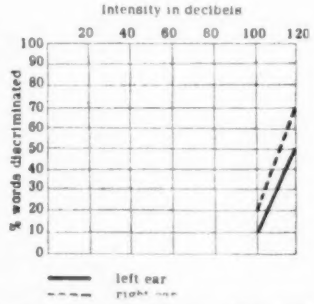

FIG. 5B.—Speech audiogram of Case III after six months' training.

this is reflected markedly in his improved motor speech ability. Like the other children, he comes from a home in which we have the full co-operation of the parents, whom we train to support us in our work. Of course, much of our success is due to their help but their co-operation is not always easily won.

The improvement in communication skills made by the children attending the Palmer Unit has led to increased social competence. The quality and quantity of their friendships is striking, e.g. Case II has 18 hearing friends with whom she plays. Her accounts of them and their activities together show a most encouraging normality which augurs well for the more distant future when she leaves school. Many of the children's early personality problems expressed in stress symptoms such as nail biting, bed wetting and temper tantrums have been overcome. Equally important, educational standards have, in most cases, been equated with those of hearing children of like age and ability. It is noteworthy that sudden spurts in attainments have regularly followed the growth of communication skills.

In conclusion, I should like to stress the

remedial nature of the work I have described with these Grade III deaf children. Remedial work was necessary only because each case suffered late diagnosis, or late or ineffective early treatment. Had the prevention of handicap been possible through effective specialist help in their early years it is unlikely that any one of them would have required more than occasional help at the junior school level providing they wore hearing aids and had advantageous seating in class.

In contrast, a further child, Case IV, who is as severely deaf as Cases I and III has little communication difficulty and works happily and equally alongside normally hearing children of her age. Through early and effective treatment speech and language were quickly developed and secondary disturbances in personal, social and educational development were avoided.

Table I summarizes the speech intelligibility

TABLE I.—SPEECH INTELLIGIBILITY RATINGS OF CASES I–IV BEFORE AND AFTER TRAINING

Case No.	Speech on admission	Speech after training	Length and type of training
I	e	a	2 years in unit
II	d	a	3 years in unit
III	e	b	6 months in unit
IV	—	a	2 years' home training by parent

Rating scale for Table I

a = easily understood on first hearing.
b = understood with difficulty on repetition.
c = most words understood on repetition.
d = few words understood on repetition.
e = no intelligible speech.

scores of Cases I–IV before and after a period of training. The recordings from which these scores were obtained were used in describing each case and to demonstrate how speech was used more accurately as speech audiometric results improved.

Dr. L. Fisch (London) showed an exhibit entitled *Deafness as Part of a Hereditary Syndrome.*

The exhibit illustrated in detail the symptoms of this syndrome (congenital deafness, white forelock, heterochromia iridium, abnormality of the inner angles of the eyelids), its histology, genetical aspects, and differential diagnosis.

A detailed account appears in the *Journal of Laryngology* (1959) **73**, 355.

Mr. I. S. Thomson (Aberdeen): The new Government transistor aid seemed physically appropriate for children by virtue of its small size, but its performance was no better than the Medresco valve aid which was designed to be of the greatest assistance to the majority of deaf persons. This was not a description of the severely deaf child. Like the valve aid, the transistor lacked automatic volume control.

The Government transistor posed three problems. Firstly, as it produced a gain of only 50 decibels, it was not powerful enough for the profoundly deaf infant who needed a gain in the nature of 70 or 80 decibels to bring him anywhere near the level of serviceable hearing. Secondly, the child with a marked upper-tone loss but good hearing for the lower tones could not use his aid without automatic volume control to prevent over-amplification of loud and painful low-tone noise. Function tests in a quiet room might show good results, but the child was reluctant to wear the aid in normally noisy surroundings such as at school. Thirdly, feed-back was very severe. A comparative test was described which showed that this was not due to badly fitting ear moulds. Children were particularly prone to feed-back because of the proximity of the microphone to the receiver ear-piece.

While some cases did do well with Government transistors, it was not considered suitable for many deaf infants and children, for whom a proprietary aid was essential.

Mr. W. Stirk Adams (Birmingham) referred to the place of the psychogalvanic and peep-show tests in the discovery of hearing capacity in early childhood. He understood the present practice in the audiometric service in Birmingham and elsewhere was to rely on the screening tests as the more reliable and workable.

It had been found that with the peep-show the child often became too interested in looking at the pictures to give a reliable response and often this became so erratic that one could usually gain more information by simply using an audiometer.

In the performance of the screening tests the personal contact with the patient was found to be much more valuable and helpful. The test sounds were selected according to the age of the child, using both high and low tones, and were those most likely to be familiar and of interest to a child of that age group. In carrying out the test one observer watched the child's reactions and kept it amused, while the other, unobserved

by the child, produced the sound stimuli from behind, or on one or other side at varying distances and intensities.

With this technique, when the child's confidence had been gained, it had been found possible to test children from a few months old, up to the age of 3 or 4. For the ages of 2 to 3 years performance tests were helpful, while reliable pure-tone audiometric charts both for air and bone conduction were frequently obtained in a child of normal intelligence as young as 2½ years.

Dr. K. P. Murphy (Reading), commenting upon Mr. Hunt Williams' suggestions concerning tonsils and adenoids, pointed out that the free field detection of minor degrees of deafness in the normal hospital clinic could be made more difficult by the quantity of ambient noise present. This was often of the order of 50 decibels and could be transitorily of even greater intensities when furniture was moved, doors slammed or instruments dropped into trays. He suggested that the use of a sound level meter during an occasional testing session might prove of value.

Dr. Murphy agreed with Dr. Sheridan that, in the case of very young babies, sounds of less than the order of 90–100 decibels produced more than 18 in. from the ear appeared to be beyond the periphery of the child's attention and pointed out that this was important both in testing and in the very early forms of auditory training.

Mr. Gavin Livingstone (Oxford) said that all hospitals which drained an area with a large population should have a special clinic for the assessment of children with a suspected hearing loss; it was up to otologists to press for this. A teacher of the deaf should be attached to each clinic to be responsible for auditory training and to help with the teaching of infants. Pædiatric and E.N.T. registrars should attend these clinics for experience. A register should be made of all "at risk" babies whose hearing should be tested and followed up.

Each of the bigger local authorities should have one or more deaf units attached to their best hearing school. More and more children with severe hearing loss were being sent to partially deaf units in hearing schools; the word "partially" should be dropped. Each deaf unit should be under the charge of a teacher of the deaf, and should be attended by all children whose hearing loss prevented them from holding their own in classes of their own age group.

Mr. H. V. Forster (Liverpool) also took part in the discussion.

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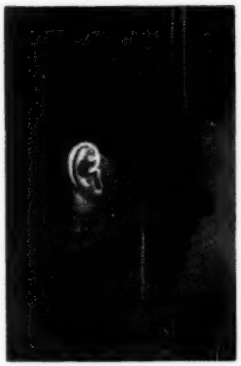

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Proceedings of the Royal Society of Medicine

Vol. 52
929

Section of Medicine

President—A. H. Douthwaite, M.D., F.R.C.P.

Meeting
May 26, 1959

THERAPEUTIC SUMMARIES

Some Aspects of New Corticosteroids

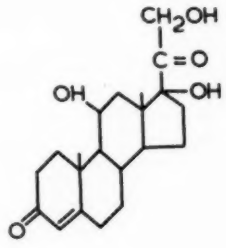
By R. I. S. Bayliss, M.D., F.R.C.P.

London

Within a short time of the introduction of cortisone ten years ago, it became clear that certain undesirable side-effects were associated with the administration of this compound. It was also clear that the incidence and severity of these side-effects were related in part to the dosage and duration of treatment, and in part to the individual response of the patient. It would be wrong to call most of these undesirable occurrences by any other name than side-effects. They should not be termed toxic because they are not the result of some toxic action but are the consequence of an increased blood level of corticosteroid hormone and some appear with equal readiness in patients with naturally occurring Cushing's syndrome. Although many different side-effects have been described, those of particular importance and consequence are: (1) Hypertension, (2) sodium retention and the formation of œdema, (3) potassium depletion, (4) osteoporosis and nitrogen depletion, (5) the development or accentuation of diabetes, and (6) peptic ulceration with hæmatemesis, melæna or perforation.

The first two of these side-effects are probably related, and the hypertension is largely dependent upon sodium retention. Osteoporosis has been attributed, according to the current orthodox view based on the work of Albright, to the anti-anabolic effect of corticosteroids on protein synthesis. However, recent work suggests that bone demineralization and collapse of vertebræ may be as much due to disturbances of calcium and phosphorus metabolism as to protein synthesis. Diabetes mellitus usually occurs in patients who already have a tendency to diminished glucose tolerance and it is doubtful if frank diabetes develops in patients with previously normal carbohydrate metabolism. Indeed Fajans and Conn (1954) have evolved a most useful test using a single dose of cortisone to uncover latent diabetes.

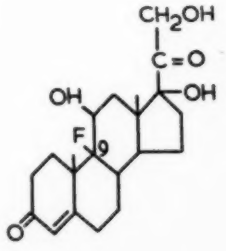
Matters might have rested in this relatively unsatisfactory state had it not been for the organic chemists who suspected that by altering the structure of the cortisone molecule they might influence its biological properties. The first product of these researches to become commercially available was hydrocortisone—the naturally occurring adrenal glucocorticoid secreted by the human adrenal and the substance to which cortisone is converted in the body.



Hydrocortisone

Although hydrocortisone proved slightly more potent than cortisone, there were no differences in the side-effects produced by the two compounds.

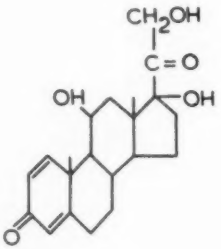
Fluorohydrocortisone.—The first major change in the biological properties of cortisone and hydrocortisone was effected by Fried and Sabo



9α-fluorohydrocortisone

(1953, 1954). They substituted a halogen atom in the 9-alpha position of the steroid molecule, and the most potent substance proved to be the fluorinated derivative of hydrocortisone. This was some ten times more potent, on a weight-for-weight basis, than cortisone in the liver glycogen deposition test—a function which seems to run closely parallel to the anti-inflammatory action of the compound. However, fluorination also increased the sodium-retaining properties of the compound to a remarkable and disproportionate degree, with the result that fluorohydrocortisone proved 100 times more potent than the parent substance in its mineralocorticoid action. Despite its enhanced antiphlogistic potency, the extreme electrolyte activity of fluorohydrocortisone precluded its systemic use as a substitute for cortisone, although it has proved most useful in the topical treatment of dermatological and ophthalmic diseases. However, its main place is as the ideal substitute for parenterally administered deoxycortone in the treatment of adrenal insufficiency (Bayliss, 1958). Many patients who have been adrenalectomized for the treatment of Cushing's disease, or for the arrest of malignancy, remain apparently well on substitution with cortisone alone, but often clinical manifestations of sodium depletion or biochemical abnormalities (a low serum sodium level and sometimes also hypochloræmia and hyperkalæmia) occur even though supplements of sodium chloride are given (Bayliss, 1958; Nabarro and Walker, 1957). These patients are immeasurably improved by the addition of a small dose of fluorohydrocortisone. The amount given must be sufficient to maintain a normal serum sodium level and not so great as to induce œdema or hypertension, although it should be remembered that in older patients the "normal" blood pressure may be greater than 120/80 and the patient feels better when the blood pressure is maintained at 150/90 mm.Hg. The usual dose required is 0·1 mg. daily or on alternate days, and the exact amount can only be determined by clinical experimentation.

Prednisolone and prednisone.—The next major change effected by the chemists was the introduction of a double bond between the first and second carbon atoms in the A ring of the steroid molecule. The resulting compounds, prednisone and prednisolone, derived respectively from cortisone and cortisol (hydrocortisone), proved to be four or five times more potent in glycogen deposition and antiphlogistic activity without any enhancement of mineralocorticoid activity. Thus the side-effects of sodium retention, potassium depletion, and hypertension—except when unusually large doses were given—were largely but not completely eliminated, and this constituted a major advance. Except in the treatment of adrenal insufficiency, prednisone and prenisolone came to replace cortisone and cortisol. But although the bugbear of œdema and hypertension had in large measure been eliminated, the other side-effects continued, with peptic ulceration and osteoporosis as the most important and troublesome.

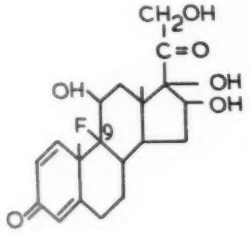


Prednisolone

Chemists continued to synthesise new compounds and such is the structure of the steroid molecule that innumerable permutations and combinations are possible although often difficult to achieve technically. The goal of this effort has been to achieve a compound with "pure" anti-inflammatory activity dissociated from anti-anabolic and ulcerogenic properties. Each compound has to be obtained in an uncontaminated state and then subjected to a long series of animal tests to determine its biological properties.

Triamcinolone.—The next development involved altering the steroid molecule at the C-16 position, and triamcinolone which is 9-α-fluoroprednisolone with a hydroxyl group at C-16 was introduced. The hydroxylation considerably changed the properties of the 9-α-fluoroprednisolone which thereby lost its mineralocorticoid activity. Triamcinolone has been widely acclaimed for its antiphlogistic activity and has been used in situations previously treated with prednisone or prednisolone. It was hoped that the incidence of side-effects would be reduced, but these hopes have not been fulfilled. In potency triamcinolone is only slightly more powerful than the $\triangle^1$-steroids and 4 mg. is usually equivalent to 5 mg. prednisone or prednisolone (Hellman *et al.*, 1957). However, dyspepsia, perforation of a peptic ulcer and osteoporosis may occur (Hollander, 1957; Hart *et al.*, 1958; Kendall and Hart, 1959; Thompson, 1959), and a series of additional and unusual

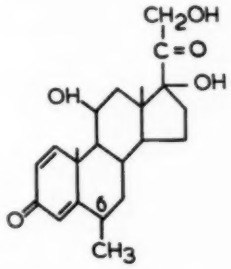
side-effects have been reported which are largely peculiar to triamcinolone, and seen only very rarely with other corticosteroids. These comprise joint pains, postprandial flushing, drowsiness, headache, loss of weight, muscular weakness particularly in the legs, and muscular wasting (Freyberg *et al.*, 1957; Hollander, 1957; Wells, 1958; Kendall and Hart, 1959). The muscle weakness may be severe, and electromyography indicates a muscle-fibre lesion; the condition is not due to potassium depletion or to increased protein catabolism (Williams, 1959). The cause of this disturbance, which is usually reversible when triamcinolone is stopped and another steroid substituted, is uncertain. It has been reported after unusually large doses of 9-α-fluorohydrocortisone and therefore attributed to the presence of a fluorine atom in the steroid molecule (MacLean and Schurr, 1959). However, Harman (1959) has observed a similar myopathy in patients treated with prednisolone, and Ellis (1956) has produced necrosis of skeletal muscle in rabbits by giving massive doses of cortisone. This side-effect is particularly likely to occur if



Triamcinolone

the dose of triamcinolone exceeds 10–12 mg. daily, which may be necessary for the control of otherwise fatal conditions such as disseminated lupus erythematosus. Weight loss is also common during triamcinolone administration (Robinson and Robinson 1959), and may be progressive and marked. These changes occur sufficiently frequently to make triamcinolone less therapeutically useful than was initially hoped. In individual cases it may prove therapeutically superior to the Δ^1-steroids but on the whole it is wiser to use prednisone and prednisolone, except in hypertensive patients and those who have developed œdema or hypertension with other corticosteroids (Thompson, 1959).

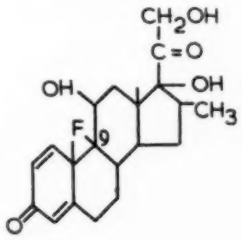
6-methylprednisolone. — Methylprednisolone was the next corticosteroid to be introduced. It differs from prednisolone in having an additional methyl group at the C-6 position. In potency it is about equivalent to triamcinolone and 4 mg. usually has an antiphlogistic effect



6-methylprednisolone

equal to 5 mg. prednisolone. However, it does not appear to share with triamcinolone the peculiar side-effects of muscle weakness and weight loss. On the other hand no clear superiority over prednisolone has been demonstrated with regard to other side-effects although it may have less effect on electrolyte balance.

Dexamethasone.—The latest addition to the synthetic corticosteroid drugs is dexamethasone which is 9-α-fluoroprednisolone with a methyl group at the C-16 position (Arth, Johnston, *et al.*, 1958; Arth, Fried, *et al.*, 1958). It is there-



Dexamethasone

fore similar to triamcinolone but differs from it in having a methyl instead of a hydroxyl group added in the D-ring. However, this change has considerably altered the biological potency of the compound, and in its anti-inflammatory effect 0·75 mg. dexamethasone is equivalent to 5 mg. prednisolone or 4 mg. triamcinolone or

methylprednisolone (Boland, 1958*a*). Thus on a weight basis dexamethasone is the most potent corticosteroid available and its enhanced antiphlogistic activity is wholely dissociated from any electrolyte effect. For example, Addisonian patients satisfactorily maintained on cortisone rapidly develop symptoms and signs of sodium depletion when switched to dexamethasone. Clinical experience confirms that sodium retention, œdema and hypertension do not occur. Nor does dexamethasone appear to cause mental depression or euphoria. Unlike triamcinolone, it has not been observed to cause muscle weakness, muscular wasting, and loss of weight (Boland, 1958*b*). Some experimental works suggest that dexamethasone does not reduce carbohydrate tolerance as readily as other corticosteroids (Bunim *et al.*, 1958; Villa *et al.*, 1958).

However, dexamethasone induces many of the same side-effects as prednisolone, such as facial mooning, buffalo hump, hypertrichosis and ecchymotic skin lesions. It has a distinct tendency to enhance appetite with a consequent increase in weight particularly marked on the abdomen. Peptic ulceration and dyspepsia occur in about the same frequency as after prednisolone.

Satisfactory results in the treatment of rheumatoid arthritis have been reported by various workers and in some instances the control of the disease has been better with dexamethasone than with prednisolone (Boland, 1958*b*; Robecchi *et al.*, 1959).

Metabolic studies have confirmed that dexamethasone does not cause sodium retention; it may even induce a sodium diuresis. Potassium excretion is not increased (Bunim *et al.*, 1958). It may, however, increase nitrogen excretion particularly when large doses are given. Loss of phosphorus and calcium also occurs (Bunim *et al.*, 1958; Slater *et al.*, 1959; Bayliss and Zilva, 1958, unpublished observations). Much of the increased excretion of calcium is found in the fæces, and this is an unusual finding not observed with other corticosteroids. It suggests that skeletal disorders may be induced during prolonged treatment with dexamethasone. Since the increased loss of calcium is mainly fæcal it occurred to us that this effect might be reversed by co-administration of vitamin D. Experimentally there is some evidence to support this, and there is some additional evidence that administration of vitamins A and D together is more effective than vitamin D alone.

The problem of peptic ulceration still remains. It is perhaps surprising that after a decade of corticosteroid therapy, there is no unanimity of opinion as to whether this ulcerogenic effect is due to a local action on the gastric mucosa or is a humoral effect. Certainly peptic ulceration is not, in my experience of more than 40 patients, a common occurrence in Cushing's syndrome, and many rheumatologists have found that the co-administration of antacids may reduce the incidence of dyspepsia. Some have suggested that corticosteroids should be administered as an emulsion. Recently trials have been started using enteric-coated tablets and preliminary results are promising.

REFERENCES

ARTH, G. E., FRIED, J., JOHNSTON, D. B. R., HOFF, D. R., SARETT, L. H., SILBER, R. H., STOERK, H. C., and WINTER, C. A. (1958) *J. Amer. chem. Soc.*, **80,** 3161.

——, JOHNSTON, D. B. R., FRIED, J., SPOONER, W. W., HOFF, D. R., and SARETT, L. H. (1958) *J. Amer. chem. Soc.*, **80,** 3160.

BAYLISS, R. I. S. (1958) *Postgrad. med. J.*, **34,** 305.

BOLAND, E. W. (1958*a*) *Calif. Med.*, **88,** 417.

—— (1958*b*) *Ann. Rheum. Dis.*, **17,** 376.

BUNIM, J. J., BLACK, R. L., LUTWAK, L., PETERSON, R. E., and WHEDON, G. D. (1958) *Arthr. & Rheum.*, **1,** 313.

ELLIS, J. T. (1956) *Amer. J. Path.*, **32,** 993.

FAJANS, S. S., and CONN, J. W. (1954) *Diabetes*, **3,** 296.

FREYBERG, R. H., BERNSTEIN, C. A., and HILLMAN, L. (1957) International Congress on Rheumatic Diseases, Toronto, 1957.

FRIED, J., and SABO, E. F. (1953) *J. Amer. chem. Soc.*, **75,** 2273.

——, —— (1954) *J. Amer. chem. Soc.*, **76,** 1455.

HARMAN, J. B. (1959) *Lancet*, i, 887.

HART, F. D., GOLDING, J. R., and BURLEY, D. (1958) *Lancet*, ii, 495.

HELLMAN, L., ZUMOFF, B., SCHWARTZ, M. K., GALLAGHER, T. F., BERNSTEIN, C. A., and FREYBERG, R. H. (1957) *Ann. Rheum. Dis.*, **16,** 141.

HOLLANDER, J. L. (1957) *Ann. Rheum. Dis.*, **16,** 142.

KENDALL, P. H., and HART, M. F. (1959) *Brit. med. J.*, i, 682.

MACLEAN, K., and SCHURR, P. H. (1959) *Lancet*, i, 701.

NABARRO, J. D. N., and WALKER, G. (1957) *Brit. med. J.*, ii, 17.

ROBECCHI, A., DANEO, V., DI VITTORIO, S., EINAUDI, G., and MARRAZI, G. (1959) *Minerva Med.*, **49,** 4163.

ROBINSON, C. E., and ROBINSON, H. S. (1959) *Canad. med. Ass. J.*, **80,** 245.

SLATER, J. D. H., HIFFRON, P. F., VERNET, A., and NABARRO, J. D. N. (1959) *Lancet*, i, 173.

THOMPSON, M. (1959) *Brit. med. J.*, i, 1259.

VILLA, L., BALLABIO, C. B., and SALLA, G. (1958) *Rheumatismo*, **3,** 127.

WELLS, R. (1958) *Lancet*, ii, 499.

WILLIAMS, R. S. (1959) *Lancet*, i, 698.

Antibiotic Therapy

By R. A. SHOOTER, M.D.

London

NINE years ago this Section held a Discussion on the present position of the newer antibiotics (*Proceedings*, 1950, **43**, 689). For treatment we still depend mainly on antibiotics which were known then, and I thought I might perhaps look at the older antibiotics before proceeding to the newer ones.

OLDER ANTIBIOTICS

Penicillin.—It is interesting that the first antibiotic to be produced should have been in many respects the safest and most effective. The value of penicillin for the treatment of infections due to hæmolytic streptococci deserves especial mention. Unlike staphylococci, Group A hæmolytic streptococci cannot become resistant to penicillin, and clinical infections respond to treatment as well as sensitivity tests suggest they should.

From a practical point of view the chief drawback to penicillin has been the very rapid rate at which it is excreted. One solution to this lay in the use of procaine penicillin. More recently penicillin V has been used. This substance is not destroyed in the stomach and for most infections provides adequate levels.

One advantage is derived from the rapid excretion of penicillin into the urine. By increasing the dose very high concentrations can be obtained, and we have sometimes found this useful in the treatment of urinary infections due to coliform bacilli.

Streptomycin is mainly used for tuberculosis, which I do not propose to discuss. In the urine it is an excellent disinfectant. It is almost useless in an acid urine and the reaction of an early morning specimen should be alkaline before treatment is begun. Using it in a non-alkaline urine is not only ineffective but also encourages the production of resistant bacteria. As the action is rapid a two-day course is sufficient, which also avoids the risks of toxic reactions.

The *tetracyclines* are true broad-spectrum antibiotics in that they inhibit the growth of a wide range of bacteria. We now have three forms on the market, with perhaps a fourth on the way. Aureomycin, or chlortetracycline, came first, to be followed by Terramycin, or oxytetracycline, in 1950. The performance of the two drugs is almost identical and is due to the tetracycline component. Tetracycline alone, under the names Tetracyn, Achromycin, is now available.

D.M.C.T., or demethylchlortetracycline is produced by a mutant of *Streptomyces aureofaciens*. A preliminary report suggests that it is more stable than chlortetracycline and that it is better absorbed and perhaps more powerful. If the early promise is fulfilled it may become the tetracycline of the future.

Another aspect of the tetracyclines has been under study. As a group the tetracyclines combine with metallic cations such as calcium, forming a compound which is poorly absorbed or not absorbed at all. If either citric acid or phosphate is given at the same time it combines with cations and so renders them unavailable for combination with the antibiotic. Experiments in animals and in men have shown that if sodium metaphosphate or citric acid is added to tetracycline, absorption is considerably enhanced.

It has also been shown that the addition of dicalcium phosphate reduces absorption. This is of interest because in the past dicalcium phosphate has been used as a filler for capsules of the tetracycline group of antibiotics, and must have detracted from their use.

Chloramphenicol.—We have been unfortunate in our experience of marrow aplasia due to chloramphenicol. This condition is probably very uncommon, but is a reason for using a less potentially toxic drug if possible. My own view of the indications for chloramphenicol would be typhoid fever, *Hæmophilus influenzæ* meningitis, and infections resistant to other antibiotics but sensitive to chloramphenicol.

Erythromycin is unique in that in this country it was the first antibiotic whose use was voluntarily restricted. The policy was directed at resistant staphylococci and has worked. In many hospitals it is still unusual to meet any number of erythromycin-resistant strains.

It is probably the right drug with which to begin the treatment of patients with staphylococcal pneumonia after influenza. This condition progresses so rapidly that it is vital to use a drug to which the staphyloccocus is sensitive as soon as possible. Table I gives the sensitivities

TABLE I.—ANTIBIOTIC SENSITIVITIES OF STRAINS OF *Staph. aureus* FROM 155 PATIENTS WITH POST-INFLUENZAL STAPHYLOCOCCAL PNEUMONIA (Oswald *et al.*, 1958)

	Strains of staphylococci acquired			
	Outside hospital		Inside hospital	
	Total	% resistant	Total	% resistant
Penicillin	113	49	27	93
Streptomycin ..	89	12	24	62
Tetracycline ..	94	22	27	74
Chloramphenicol ..	96	6	23	9
Erythromycin ..	60	7	25	4

of staphylococci isolated from a series of 155 patients with staphylococcal pneumonia following the Asian 'flu epidemic. Whether the influenza was contracted at home or in hospital an appreciable number of staphylococci were resistant to penicillin, streptomycin and tetracycline. If it is decided to give erythromycin, it is probably best to start with intravenous doses, in view of possible irregularities in absorption.

Combined treatment.—Recently it has become popular to use two antibiotics at a time. There are several possible reasons for doing this; two of them I would like to look at for a moment.

The usual reason for combining two antibiotics is the hope that by doing so the chance of producing resistant bacterial strains will be reduced. In the test tube there is no doubt about this and the reason is clear. It is that when a resistant strain is produced it will usually be resistant to one or other of the two drugs employed. The chance of producing a variant which is resistant to both antibiotics at once is much less.

This policy is accepted in the treatment of tuberculosis, and the slow rate of growth of the tubercle bacillus may contribute to its success. Among infections caused by faster growing bacteria, those due to staphylococci have most frequently been treated with two antibiotics at a time.

There are some suggestions that using 2 drugs together delays the appearance of resistant staphylococci. I personally feel that it is optimistic to hope that resistance can for long be suppressed in this way. When two antibiotics mix in a test tube the mixture is complete, but in the body there must be situations where the drugs used are present in very unequal amounts.

The other reason for using two antibiotics together is that by so doing a synergistic action is produced. An often-quoted example shows the action of penicillin and streptomycin on a strain of *Streptococcus fæcalis*. Penicillin did not kill this variety of streptococcus completely and after forty-eight hours the surviving bacteria began to grow. This particular streptococcus was not sensitive to streptomycin at all, and it even multiplied in the presence of 25 μg./ml. But when penicillin and streptomycin were used together the combination was bactericidal and in forty-eight hours all the streptococci were killed.

As usually reported, sensitivity tests are a guide to the ability of an antibiotic to inhibit growth only. They do not test the capacity to kill bacteria which has to be tested for separately. Tests of this sort are very well worth doing in the treatment of patients with endocarditis, as in this condition the patient's own defences cannot be relied on to deal with even small numbers of bacteria and treatment should aim at killing all. It is doubtful if there are many other conditions in which bactericidal antibiotics or combinations of antibiotics are essential. Among the possibilities are perhaps some staphylococcal infections and urinary infections.

Resistance

Staphylococci have shown a quite remarkable ability to develop resistant strains to one antibiotic after another and there is even a suggestion that some antibiotic-resistant staphylococci have a greater capacity for producing disease. These resistant strains have been found all over the world and their occurrence is linked to the amount of antibiotic prescribed.

Another aspect of resistance is the fairly recent discovery of penicillin-resistant gonococci. It has long been possible to make gonococci resistant to penicillin in the test tube, and it is fortunate that the emergence of naturally occurring resistant strains has been delayed. Of 200 strains examined recently we found that 38 required the quite high figure of 0·128 units/ml. for inhibition. Similar findings have been made in this country and elsewhere. The laboratory findings were borne out in the results of treatment: of the 38 patients with resistant strains, 13 relapsed, while from the 162 patients with sensitive strains 12 relapsed. The degree of resistance is not of course great, and can be overcome by increasing the dose of penicillin. One additional observation was made. After an interval of some ten years in which sulphonamides have not been used in the treatment of gonorrhœa, instead of 80% or so of resistant strains, only 1 strain was found to be resistant.

Some New Antibiotics

Most of these new antibiotics have been welcomed as new drugs for the treatment of staphylococcal infections.

Erythromycin group.—There are several antibiotics which have a range of activity resembling that of erythromycin, that is they will inhibit the growth of many Gram-positive organisms and some of the more delicate Gram-negative bacteria such as neisseria and hæmophilus.

This is of course also the penicillin range, and these drugs—as indeed erythromycin—are most likely to be used for infections due to penicillin-resistant bacteria, or for patients sensitive to

penicillin. In practice by far the commonest penicillin-resistant bacteria are staphylococci.

The action of carbomycin resembles that of erythromycin very closely, except that it is at a lower level, and less is absorbed. It is not therefore a close competitor. Spiramycin was discovered in France and is available in this country as Rovamycin. *In vitro* it is considerably less active than erythromycin. Oleandomycin, an American antibiotic, is more active than spiramycin but has only about a quarter the strength of erythromycin. The poorer performance of oleandomycin is partially compensated for by the greater absorption and hence higher blood levels obtained with triacetyl oleandomycin. In turn the last preparation on the list—erythromycin ester—gives promise of producing higher blood levels than erythromycin.

There is a considerable degree of cross-resistance within this group although, for staphylococci, strains occur which are resistant to one member of the group but not to another. In the absence of some indication based on resistance erythromycin seems to be the most obvious antibiotic in the group to employ.

Novobiocin is a separate antibiotic on its own, with again a range of activity which includes many Gram-positive bacteria. It has been most useful, perhaps, in the treatment of resistant staphylococcal infections. Staphylococci develop resistance to novobiocin fairly readily, but before they do so, it is a useful additional antibiotic to have on call.

Vancomycin is also a separate antibiotic and one of considerable interest, because unlike those reviewed so far, it is both bacteriostatic and bactericidal. It has two disadvantages. Present preparations are not absorbed from the gut, cannot be given intramuscularly, and so have to be given intravenously. As Dutton and Elmes (1959) have shown, in uræmic patients the amount of vancomycin in the blood may rise to a level at which the VIII nerve is damaged and deafness produced.

Vancomycin is active mainly against Gram-positive organisms, and because of the difficulties of administration, it has been used chiefly in hospitals for the treatment of serious infections due to resistant staphylococci. Staphylococci apparently rarely become resistant to vancomycin and there is no known link of cross-resistance with other antibiotics. Provided it is kept for suitable patients and provided the blood concentration can be controlled, vancomycin looks like being a useful addition to the list of antibiotics.

Ristocetin is another new antibiotic, with a limited spectrum of activity which is practically confined to Gram-positive bacteria. Resistance is not readily acquired, and cross-resistance with other antibiotics has not been reported. It also has to be given intravenously, and its use is likely to be restricted to serious conditions caused by bacteria resistant to other antibiotics.

Neomycin is not a new antibiotic in the sense the others I have mentioned are, as it was discovered in 1949. It is active against a wide range of Gram-positive and Gram-negative organisms, although streptococci are relatively resistant. It is not absorbed from the gut and when given parenterally is liable to cause deafness. For this reason it was at first put to one side. In the last few years it has come back for a few restricted uses.

As it is not absorbed from the gut and has a wide range of activity, it is a good antibiotic to use before operations on the bowel. It may in some cases be too good in that the normal flora is removed with such success that staphylococcal enterocolitis follows. It has also been used for the treatment of nasal carriers of staphylococci.

Finally there is probably a place for neomycin in the treatment of urinary infections. With sensitive bacteria and in an alkaline urine its action is very rapid. Three doses of 0·5 gram spread over thirty-six hours will be enough if neomycin is going to be effective, and in the absence of gross renal damage, there is virtually no risk of deafness with this dose.

REFERENCES

DUTTON, A. A. C., and ELMES, P. C. (1959) *Brit. med. J.*, i, 1144.

OSWALD, N. C., SHOOTER, R. A., and CURWEN, M. P. (1958) *Brit. med. J.*, ii, 1305.

Professor J. MCMICHAEL (London) read a paper on **Hypotensive Therapy** (*See* Harington, M., Smith, K., and McMichael, J., 1959, *Brit. med. J.*, ii. In press.)

BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

Alexander (F. M.). Man's supreme inheritance. 3rd ed. pp. 214. London: Chaterson. 7s. 6d. 1946.

Atkins (R. T.), and **Atkins (J. McG.).** The world traveler's medical guide. pp. 399. New York: Simon and Schuster. $1.95. 1958.

Axenfield (T.). Lehrbuch und Atlas der Augenheilkunde. 10te Aufl. pp. 786. Jena: Fischer. 1958.

Barcelona. Instituto Barraquer. 1. Curso internacional de oftalmologia. 2 vols. Barcelona: Instituto Barraquer. 1956.

Blackley (C. H.). Experimental researches on the causes and nature of catarrhus aestivus (hay-fever or hay asthma). pp. 202. London: Dawson. 1873 (reprinted 1959).

Bredow (M.). The medical assistant: a guide-book for the nurse, secretary, and technician in the doctor's office. pp. 439. New York, etc.: McGraw-Hill. 58s. 1958.

Brod (J.). Chronische Pyelonephritis. pp. 130. Berlin: Verlag Volk und Gesundheit. 1957.

Brugsch (J.). Porphyrine. 2te Aufl. pp. 221. Leipzig: Barth. 1959.

Cantril (S. T.). Radiation therapy in the management of cancer of the uterine cervix. pp. 196. Springfield, Ill: Thomas. 1950.

Central Office of Information. Social Services in Britain. 2nd ed. pp. 75. London: H.M.S.O. 3s. 6d. 1956.

Costantini (A.), and **Aglio (E. d').** Lo svuotamento anomalo dell vene polmonari. pp. 188. Pisa: Omnia Medica. L.2000.

Diehl (H. S.). Healthful living. pp. 529. New York, etc.: McGraw-Hill. 45s. 1955.

Doederlein (G.). Die Behandlung entzündlicher Genitalerkrankungen der Frau. 4te Aufl. pp. 148. Leipzig: Thieme. 1959.

Duren (A.). L'Organisation médicale belge en Afrique. pp. 92. Brussels: Académie Royale des Sciences Coloniales. 1955.

Eichner (H.), and **Hein (H.).** Reading German for scientists. pp. 207. London: Chapman and Hall. 30s. 1959.

Fischer (W.), and **Kuehl (I.).** Geschwülste der Laboratoriumsnagetiere. pp. 260. Dresden: Steinkopff. 1958.

Fromme (A.). Das Mesenchym und die Mesenchymtheorie des Karzinoms. pp. 270. Dresden: Steinkopff. 1953.

Garrett (E. J.). Telepathy: in search of a lost faculty. pp. 210. New York: Creative Age Press. 1945.

Gibson (J. M.). Soldier in white: the life of General George Miller Sternberg. pp. 277. Durham, N.C.: Duke University Press. 51s. 1958.

Graffi (A.), and **Bielka (H.).** Probleme der experimentellen Krebsforschung. pp. 560. Leipzig: Geest und Portig. 1959.

Hall (I. S.). Diseases of the nose, throat and ear. 7th ed. pp. 467. Edinburgh and London: Livingstone. 21s. 1959.

Holand (H.). House of open doors. pp. 257. Milwaukee: Wisconsin Anti-Tuberculosis Association. 1958.

Hutyra (F.), and **Marek (J.).** Spezielle Pathologie und Therapie der Haustiere. Bearbeitet von Rudolf Manninger und Johannes Mócsy. 11te Aufl. 2 vols. Jena: Fischer. 1959.

James (D. G.). The diagnosis and treatment of infections. pp. 234. Oxford: Blackwell. 30s. 1957.

Kneise (O.), and **Schober (K. L.).** Die Röntgenuntersuchung der Harnorgane. 5te Aufl. pp. 326. Leipzig: Thieme. 1958.

Lickint (F.). Ätiologie und prophylaxe des Lungenkrebses als ein Problem der Gewerbehygiene und des Tabakrauches. pp. 212. Dresden: Steinkopff. 1953.

Mackey (H. O.). A handbook of diseases of the skin. 6th ed. pp. 263. London: Macmillan. 8s. 6d. 1959.

Malcolm (J. E.). Blood pressure sounds and their meanings. Part 2: Ætiology of melanotic cancer. pp. 70. London: Heinemann. 12s. 6d. 1959.

Mazzacurati (T.). La venerologia del tombolo. pp. 166. Pisa: Omnia Medica. L.2000. 1959.

Minney (R. J.). Viscount Addison: Leader of the Lords. pp. 256. London: Odhams Press. 25s. 1958.

Parke, Davis and Company, Limited. A history of medicine in pictures. 1st and 2nd series. Michigan: Parke, Davis & Co. 1957–1958.

Peiper (A.). Chronik der Kinderheilkunde. 3te Aufl. pp. 527. Leipzig: Thieme. 1958.

Pintus (G.), Muratorio (A.), and **Giannini (A.).** Le sindromi neuropsichiche da carenza alimentare. pp. 289. Pisa: Omnia Medica. L.3000. 1959.

Pooler (H. W.). My life in three counties. pp. 247. London: Christopher Johnson. 15s. 1950.

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President—Sir WELDON DALRYMPLE-CHAMPNEYS, Bt., C.B., M.A., D.M., F.R.C.P.

Meeting
June 3, 1959

Wives of Some Famous Doctors

PRESIDENT'S ADDRESS

By Sir WELDON DALRYMPLE-CHAMPNEYS, Bt., C.B., M.A., D.M., F.R.C.P.
London

IT will be generally acknowledged that the home of any man doing important work must have a profound effect upon his activities, the quality of his work and his opportunities of influencing his contemporaries. This will be especially true of a doctor, since much of his work is usually done in his own home—or at any rate was in the past. Yet when we come to examine the biographies of great doctors we find that information with regard to their wives is, with some notable exceptions, poor and scattered.

It was for this reason that I thought a short consideration of the lives of some famous doctors' wives might be of interest, though I lay no claim to the discovery of facts unknown to the more erudite of my readers.

In selecting the six subjects of these short memoirs I have given preference to those ladies who either had some personal claims to distinction, or who seem to have played an important, though often unobtrusive, part in the blossoming of their husbands' genius. The ladies selected exercised such influence in varying ways and I was at first tempted to group them according to the nature of their catalysis, but finally decided that a chronological order would be more natural and helpful.

MARGARET CLEMENT (OR CLEMENTS)

Dr. John Clement was born at the very beginning of the sixteenth century, though the actual date of his birth is unknown. He was probably a native of Yorkshire, was educated at St. Paul's School, and was taken at an early age into that delightful family, of which we are fortunate to have such vivid descriptions, the household of Sir Thomas More. One member of that household was Margaret Giggs, a young kinswoman of Sir Thomas whom he brought up with his own daughters, and she became by no means the least learned member of that learned family. More describes her as "verye wyse and well learned, and very vertuous too". In the selection of her favourite study, algebra, she must, I think, have been almost unique among her sex, at any rate until modern times. Judging by Holbein's drawing of her head (Fig. 1) preserved in the royal collection, she was not

FIG. 1.—Margaret Clement. An engraving by Bartolozzi (in the possession of the Royal College of Physicians), from a drawing by Holbein.

physically beautiful, but John Clement obviously found her attractive in other ways and after their marriage in about 1530, her devotion, aided no no doubt by her wisdom and unwavering faith both in her religion and in her husband's virtues and attainments, must have been of inestimable succour to him in his distinguished but disturbed career. Moreover More tells us, in his "Second Booke of a Dyalogue of Comfort against Tribulacion", that Margaret studied "physicke" and helped him when he had a tertian fever during his imprisonment in the Tower and his two physicians were baffled, so she probably helped her husband in his medical as well as his classical studies.

She was nurse to the boy who later became King Edward VI, and the name "Mother Jak", which appears on Holbein's portrait is thought to have been his pet name for her.

If this was the case, however, his affection did not promise sufficient protection for her husband when, on the boy's succession, he felt bound to leave the country "for religion's sake"—he being ever a devoted adherent of the old faith—and retire to Louvain. Their troubles had, however, started earlier with the martyrdom of their beloved patron, Sir Thomas More, in 1535. On the day before he suffered he sent back to Margaret Clement an "algorisme stone" of hers which he had with him in the Tower, and she managed to obtain the shirt worn by him at his execution, which she lovingly preserved. One other souvenir of hers of this sad occasion is on record, namely the letter of Sir Thomas Elyott conveying to John and Margaret Clement the indignation felt by Charles V at More's execution.

When Mary ascended the throne the future looked more rosy for members of the old faith and the Clements returned to England on March 19, 1553 (or 1554), John setting up in practice in Essex. This respite was not, however, a long one as on Elizabeth's succession they were again impelled to go abroad, this time to Mechlin, where Margaret died on July 6, 1570, her husband surviving her by two years. They had one child, a daughter, Winifred, who married William Rastall, Sir Thomas More's nephew, who became a judge.

Elizabeth Harvey

About my next subject, Elizabeth Harvey, very little is, unfortunately, known, but I find myself naturally, but I admit quite illogically, unwilling to pass by without comment the wife of one who means so much to us all. Elizabeth was the daughter of Dr. Lancelot Browne, physician to Queen Elizabeth I and King James I. She was born in 1580, and on November 24, 1604, she was married to Dr. William Harvey, she being then 24, and belonging to the parish of St. Sepulchre's, whilst he was 26 and belonged to St. Martin's, Ludgate. She is said to have been "tall, of a dark complexion and somewhat severe aspect". A few weeks before their marriage William had been admitted a Member of the College of Physicians. Elizabeth's father, Dr. Browne, died the year after their marriage. I hope there may be a few readers who are not familiar with Harvey's story of his wife and her pet parrot, because I cannot resist recounting it once more.

"A parrot", he wrote, "a handsome bird and a famous talker, had long been a pet of my wife's. It was so tame that it wandered freely through the house, called for its mistress when she was abroad, greeted her cheerfully when it found her, answered her call, flew to her, and aiding himself with beak and claws, climbed up her dress to her shoulder, whence it walked down her arm and often settled on her hand. When ordered to sing or talk, it did as it was bidden, even at night and in the dark. Playful and impudent, it would often seat itself in my wife's lap to have its head scratched and its back stroked, whilst a gentle movement of its wings and a soft murmur witnessed to the pleasure of its soul. I believed all this to proceed from its usual familiarity and love of being noticed, for I always looked upon the creature as a male on account of its skill in talking and singing (for amongst birds the females rarely sing or challenge one another by their notes, and the males alone solace their mates by their tuneful warblings) . . . until . . . not long after the caressings mentioned, the parrot, which had lived for so many years in health, fell sick, and by and by being seized with repeated attacks of convulsions, died, to our great sorrow, in its mistress's lap, where it had so often loved to lie. On making a post-mortem examination to discover the cause of death I found an almost complete egg in its oviduct, but it was addled."

There seems no doubt that Harvey's marriage to the daughter of such an influential physician as Dr. Browne must have been of great help in the early part of his career, especially as Dr. Browne had a very high opinion of his son-in-law's attainments. William and Elizabeth were apparently a very happy couple, for he refers to her in his will as his "deare deceased loving wife" and no doubt she had a soothing influence upon

him when from overwork, or ignorant opposition to his views, he was in an irritable state.

The date of Elizabeth's death is uncertain, but she was certainly alive in 1645, when her brother-in-law, John Harvey died and left her £100, and she must have died soon after this as she did not accompany William to Oxford with the Court. The Harveys had no children.

Anne Hunter

Of Anne Hunter fortunately far more is known; she was not only an interesting person in her own right, but made her husband happy, in spite of the wide differences in their origin and interests. Anne was born about the year 1742, the daughter of Robert Boyne Home, surgeon to the Royal Welsh Volunteers and from July 21, 1760, to Burgoyne's Regiment (16th Dragoons). He was also at one time surgeon to the Savoy (at that time a military prison) and lived in later life at Greenlaw Castle, Berwickshire. It was probably during the time that John Hunter served with Home in Burgoyne's Regiment that he met Anne. At any rate they are said to have been engaged for many years before they married at St. James', Piccadilly at 8 a.m. on Sunday, July 22, 1771. After a few days' honeymoon in the country they returned to the house in Jermyn Street, where John had been living since 1768 and which had formerly belonged to William Hunter, John's brother. William, having lost his fiancée some years before, was out of humour with marriage, and remained so, and this is reflected in John's letter to his brother on the eve of his marriage:

"Dear Brother, To-morrow morning at eight o'clock and at St. James' Church, I enter into the Holy State of Matrimony. As that is a ceremony which you are not particularly fond of, I will not make a point of having your company there. I propose going out of Town for a few days; when I come to Town I shall call upon you. Married or not married, ever yours, John Hunter."

John was 43 at the time of his marriage and Anne only 29; he was uncouth in his ways (though her refining influence seems to have become evident quite quickly) and fond neither of general company nor polite converse, whereas Anne loved entertainment and the arts and was a far from contemptible poet and musician. Her "Flower of the Forest" was much appreciated when it appeared in the Edinburgh magazine *The Lark* in 1765, and she wrote the well-known song "My Mother Bids Me Bind My Hair," which was set to music by her friend Haydn, whilst in return she wrote the words for his "Creation". Her "Sports of the Genii", written in 1797, to a set of graceful drawings by Miss Susan Macdonald, are said to display, in addition to natural feeling and simplicity of expression, both humour and fancy. She was a friend of Mme. D'Arblay and Mrs. Montagu

Fig. 2.—Anne Hunter. From a portrait by John James Masquerier (photograph by R. B. Fleming & Co. Ltd., in the possession of the Royal College of Surgeons).

and after her marriage musical and artistic friends flocked to the house in Jermyn Street, of which more anon.

Added to these differences of age and taste the eccentricities of genius, which surely were seldom more marked than in John Hunter's case, would have been sufficient to alienate any wife less devoted and understanding than Anne. The famous house he had built at Earl's Court, which not only satisfied this countryman's longing for fresh air and pleasant natural surroundings, but also gave him the facilities essential for his zoological and anatomical studies, was, in spite of its charming interior decorations, hardly

the ideal setting for a lady of taste and refinement, for under it was the den where anything from the Irish giant's body to that of a whale might at any time be dissected or rendered down, whilst the 6-ft.-deep area surrounding the house was the abode of a great variety of smaller animals and the mound in the grounds housed the larger fauna. So Anne, assailed by unpleasant smells from below and serenaded at night by the howling of jackals, the roaring of lions, the coughing of leopards, and the bellowing of the famous bull, might well have found life intolerable. But, we are told, this wonderful wife was so fond and proud of her husband that though she used occasionally to kick up a row if any preparation with an extra effluvium about it was left on the dissecting table, yet she enjoyed seeing him pleased with his pursuits and they were very happy together.

All we know of John Hunter, however, suggests that he must sometimes have been impatient at the disturbance of the quiet necessary to his work caused by Anne's entertainment of her friends and therefore, allowing for some exaggeration and perhaps even malice, there is probably some truth in Ottley's story that "On returning late one evening after a hard day's fag, Hunter unexpectedly found his drawing-room filled with musical professors, connoisseurs and other idlers, whom Mrs. Hunter had assembled. He was greatly irritated, and walking straight into the room addressed the astonished guests pretty much in the following strain: 'I knew nothing of this kick-up, and I ought to have been informed of it beforehand: but as I am now returned home to study I hope the present company will retire?' This intimation was, of course, speedily followed by an *exeunt omnes*".

In the summer of 1783 the Hunters moved to the house he had built in Leicester Fields, on the East side of what was later Leicester Square. Here they had a great drawing-room, furnished with beautiful and expensive furniture, a room which on the nights when Anne entertained was ablaze with candles and crowded with musicians, wits and social lions. The house at Earl's Court was lived in for only two or three months of the year, during which period John came to London each morning, but returned in time for dinner. Here the drawing room was on the ground floor, opening into a conservatory. The best bedroom, on the first floor, had panels enriched with drawings representing Cupid and Psyche, finished in water colours with true classical chastity by a near relative of Anne's.

As their married life progressed Anne's happiness became more and more clouded by anxiety for her husband. It was not merely that he took terrible risks—as witness his practice of wrestling with the bull the Queen had given him, which once very nearly cost him his life, or his pursuit and capture of his two escaped leopards—but the cumulative effect of overwork resulting in increasingly frequent attacks of angina, aided probably by the late effects of his self-inoculated syphilis, which he thought he had cured by three years' treatment with mercury. She had, then, the terrible distress of watching his health being steadily ruined and expecting his death at any time. When the blow finally came in 1793, she was left ill provided for and depended for a time on the Queen's Bounty and the generosity of Dr. Maxwell Garthshore, whom her husband had always regarded with good-natured contempt. This kind man engaged her as companion to two young ladies of fashion, his wards. It was not until 1799, when Parliament voted £15,000 for the purchase of the Hunterian Museum, that Anne was again placed in fair circumstances.

The Hunters had four children, John Banks, born June 11, 1772, died November 1838; Mary Ann, born December 12, 1773, died 1776; James, born November 1774, died February 1775; and Agnes Margaretta, born January 9, 1776, died January 30, 1838.

I cannot conclude this note better than by quoting Anne's epitaph to her husband, written eleven years after his death, for a memorial tablet at St. Martin's-in-the-Fields.

Here rests in awful silence, cold and still,
One whom no common spark of genius fired;
Whose reach of thought Nature alone could fill,
Whose deep research the love of Truth inspired.

Hunter! if years of toil and watchful care,
If the vast labours of a powerful mind
To soothe the ills humanity must share,
Deserve the grateful plaudits of mankind—

Then be each human weakness buried here
Envy would raise to dim a name so bright:
Those specks which in the orb of day appear
Take nothing from his warm and welcome light.

Agnes Lister

The story of Lady Lister begins naturally in September 1853 when young Joseph Lister, after taking the B.A. degree of the University of London and recuperating in Ireland from a sub-

sequent illness, arrived in Edinburgh and soon after called on the famous surgeon James Syme with a letter of introduction. The welcome he received from that great and amiable man not only profoundly influenced the whole of his subsequent career, but introduced him to the family circle at Millbank, Syme's House, in which he found his future wife. A mutual attachment arose between Joseph Lister and Syme's eldest daughter, Agnes, from an early period in their acquaintance and this gradually deepened until by the end of July 1855 love was so fully dominating his thoughts as to interfere with his work at a critical stage in his career. Fortunately this problem was shortly afterwards resolved by Agnes accepting his suit, upon which "he returned to his work with redoubled energy and a peaceful mind".

Nevertheless this projected marriage had brought with it the necessity for a difficult decision, for in those days the marriage of a Quaker to one of another denomination involved either resignation from the Society of Friends or disownment by them. It therefore says a good deal for the broad-mindedness of Lister's very serious father, or perhaps for his profound faith in his son, that the family's misgivings were laid aside and the paternal blessing conferred on the son, who resigned his membership of the Friends and eventually became a member of the Episcopal Church.

The marriage of Joseph Lister and Agnes Syme took place on April 23, 1856, in the drawing room at Millbank, in accordance with the Scottish custom of the time, and the young couple spent their honeymoon at the English Lakes and at Upton House, the large Queen Anne house in Essex in which Joseph Lister had been born on April 5, 1827. They then embarked on a three months' tour of the Continent in order to visit the most famous medical schools and to improve Joseph's knowledge of German and Italian. The Listers returned to Edinburgh in October 1856 and settled into their newly furnished house at No. 11 Rutland Street with great satisfaction.

That Agnes was not merely a good housewife, but also an invaluable amanuensis is vividly revealed in a letter of hers describing the last-minute preparations for Joseph's lecture on "Spontaneous Gangrene", delivered before the Medico-Chirurgical Society of Edinburgh on March 18, 1858. As usual, Joseph had left the completion of his lecture to the last moment—a curious trait in one otherwise so intensely methodical.

"We had a great drive at the end", she writes. "When we went to dinner the paper was in a most incomplete state, and it required considerable exercise of faith to believe that an hour's more work could bring it nearly to a close. However, about 7 we resumed our labours, and how we did work! Joseph's dictating was really wonderful—keeping me writing as fast as I possibly could, and the sentences flowing out so smoothly, hardly a word having to be altered. About ½ past 7 we sent for Mr. Craig, whom I have mentioned in a former letter as assisting Joseph. He was fortunately disengaged and came speedily. Joseph, still keeping my pen fully employed, instructed Mr. Craig in the preparation of the *trotters*! [the paper was illustrated by demonstrations of the state of the blood in sheep's feet] and afterwards gave him a quotation from the 'inflammation' paper to copy. At last, at 10 minutes past 8, a cab was sent for, a note or two jotted down for part of the conclusion of the paper, some of it not even noted—and off went Joseph and the manuscript, Mr. Craig and the trotters, in the cab, and arrived at the 'George Street hall' just as Dr. Haldane (who had a communication to read before Joseph's) sat down!! So he had only time to take off his great coat and at once begin."

FIG. 3.—Agnes Lister. Reproduced from Godlee (1924) by kind permission.

That this is too modest an account of Mrs. Lister's labours is shown by Joseph's letter written to his father the next day in which he mentions that she wrote for seven hours one day and eight the next, and "was most helpful in suggestions as to words and arrangements of sentences".

In 1860 we get another glimpse of Mrs. Lister's thought for him. On March 9 of that year Lister, who had just been appointed third occupant of the Chair of Surgery at Glasgow University, was required, at very short notice, to deliver a Latin thesis at his formal induction. This time the last-minute rush was not his fault, as he was only informed of the date on the morning of the day before the ordeal, to take place at 3 p.m., and was unable to start working on it until the evening or to put pen to paper until 2 a.m. on the actual day. When he took the train that morning only two-thirds was written and, as he wrote to his father, "by Aggie's suggestion, I took a Latin dictionary with me in a small carpet bag, and in the railway carriage accomplished the rest, fortunately not requiring the dictionary much". The opening of his first winter session was another important event and Mrs. Lister, writing to her mother-in-law on the day, after describing the newly decorated lecture theatre, continues "now it is just about 12. Oh! I trust he may be blessed, and believe he will be. His gown will be going on for the first time except when I saw it tried on here. About 5 minutes past! he will be beginning, and how is he getting on?"—quite admirably, as it happened.

She took in her stride the complications attending Joseph's experiments, which despite his preoccupation with practice and lectures he managed to continue, and in 1862 we find her writing "another calf was brought in on Saturday, but Joseph could not be ready to make use of it that day, so we kept it in the wash-house till Tuesday evening. Then a good many experiments were made". Nine years later, when they had returned to Edinburgh to a strenuous but less exacting life than in Glasgow, she writes to a sister-in-law "Joseph has only just come from the hospital at 4.15! and we are going to have lunch! He has had to perform two amputations at the Infirmary and on coming home finds people waiting for him (there was only one party) whom he is seeing now without having had lunch. He has an operation in private at 4.30! and three patients to see afterwards. Dr. Bishop, his private assistant, is in bed with bronchitis. Joseph had an operation before going to the hospital. So it has been a busy day".

I must regretfully omit many records in Agnes Lister's hand of her husband's triumphs at home and abroad, in all of which she took a profound interest and pleasure, and proceed to 1893 when they took their usual spring holiday, this time at Rapallo, botanizing and thoroughly enjoying themselves. Then one morning after breakfast, when they had been there about a week, Lady Lister, who was apparently in good health, had a rigor, which marked the onset of an attack of pneumonia which developed with alarming rapidity and four days later, in spite of the devoted attentions of an Italian doctor, she died.

Thus Lister lost the sole intimate companion of his life for thirty-seven years, for they had no children, one who had been not only a wife but a mother to him, who had entered into all his scientific work with humility but rare understanding, had helped him clerically and with wise advice, tirelessly, patiently, proudly and lovingly. At the beginning of their life together Dr. John Brown, referring to an illness of Agnes' childhood said "As for Agnes, she was once in Heaven for three or four days when she was a very little child, and she has borne the mark of it ever since".

Grace Revere Osler

Lady Osler is the only subject of these notes whom I knew personally, for Sir William, a friend of my father, was Regius Professor of Medicine in my time at Oxford.

Grace Revere was born in Boston on June 19, 1854, the second child and elder daughter of John Revere and Susan Tilden Torrey. Her father, an employee of the Copper Company, of which he eventually became President, was of Huguenot stock, his great-grandfather Paul Revere (the name was originally Apollos Rivoire, but he had changed it "on account the Bumpkins should pronounce it easier") having been sent to Boston by his Uncle Simon because he could find no suitable opening in life for him in Guernsey. As a small girl at the time of the Civil War Grace attended a school in Boylston Street, Boston, kept by a Miss Catherine Tilden, a distant relative, and from the age of 10 to 18 she was a pupil at Miss Foote's private school in the same town, where she acquired from her mistress an ardent love of English ways and

traditions which lasted all her life and extended to the use of many English phrases and the English spelling of words in preference to the American usage. At this school she was taught the importance of letter writing, in which she developed a characteristic clear, pungent and witty style. From her mother she acquired a thorough knowledge of housekeeping and this, combined with a very retentive memory, especially for names, was of the greatest value to her and her two husbands in later life. She is said in her youth to have been generally acknowledged as a beauty, and this picture of her (Fig. 4), taken in her old age, when I knew her, will, I think, convince you of the possible justice of such a judgment. She is described as "a tall graceful fair-haired girl with pretty features, blue eyes in which there was a sparkle of fun, and the loveliest pink and white complexion". She combined dignity with a sense of humour and enjoyment of the ridiculous, and she hated pretence.

At the age of 21, when she was staying with family friends, the Pauls, in Philadelphia, she met Dr. Samuel Gross, whom she married on December 19, 1876, in Boston, he being a distinguished surgeon of Dutch origin and seventeen years older than his bride. Dr. Samuel Gross's father, Samuel David Gross, was a pioneer of surgery who had written a famous "System of Surgery", a classic in America for thirty years. He was a widower at this time and took a great fancy to Grace, who often acted as hostess in his house. Grace was an inspiration to her husband, whose best work was done after his marriage. He was a convinced advocate of early operation for malignant tumours, at a time when general pessimism with regard to these conditions prevailed. Not only was his wife a most successful hostess, but she was tireless in her charitable work, in public and private. In 1881 she paid her first visit to England, accompanying her husband and father-in-law to the Seventh International Medical Congress in London and going on later to Oxford, where they stayed with Sir James and Lady Paget and attended a dinner at which the Prince and Princess of Wales (later King Edward VII and Queen Alexandra) and the future Kaiser were present.

The Grosses' married life was as short as it was happy, for in the spring of 1889 Dr. Gross was stricken down by a virulent type of pneumonia and died after a short illness on April 16, aged 52.

Five years earlier Dr. Gross had persuaded Dr. William Osler, already well known, to leave Montreal for the Chair of Clinical Medicine in the University of Pennsylvania and he had become a frequent guest at the Gross home. At the time of Dr. Gross's death Osler was preparing to leave Philadelphia for Baltimore, where he had been appointed Chief of the Medical Department of the Johns Hopkins Hospital. After moving to Baltimore he found time to visit Philadelphia at intervals, in spite of being very busy organizing his department and writing his famous textbook, and it appears to have been Mrs. Gross, to whom during this period he became engaged, who persuaded him to post-

FIG. 4.—Grace Revere Osler—on the terrace at 13 Norham Gardens. Reproduced from Muirhead (1931) by kind permission.

pone their marriage until the book was finished. The story is told that on the day of its publication, February 24, 1892, Osler, with a copy of it under his arm, entered the house of mutual friends in Baltimore with whom Grace was staying and throwing the book into her lap exclaimed "There, take the darn thing! now what are you going to do with the man?" Their marriage took place on May 7, 1892, Osler being then 40 and his bride nearly 38. It was an ideal marriage in which, as in other cases described in these memoirs, the wife, realizing her husband's greatness and the inestimable benefits he was con-

ferring on mankind, was content that he should put his work first and was glad and proud to be the creator of the happy home from which he constantly drew strength and to which he never returned without finding inspiration, understanding and consolation. Osler's philosophy of marriage is set forth in a letter to a young doctor about to marry. "There must be trust, gentleness and consideration. A doctor needs a woman who will look after his house and rear his children, a Martha whose first care will be for the home. Make her feel she is your partner arranging a side of the business in which she should have her sway and her way . . . console her and take her advice about the house and children and keep to yourself as far as possible the outside affairs relating to the practice." And again in his address entitled "The Student Life" he writes "What about the wife and babies if you have them? Leave them! Heavy as are your responsibilities to those nearest and dearest, they are outweighed by the responsibilities to yourself, to the profession and to the public. . . . Your wife will be glad to bear her share in the sacrifice you make"—and she was, for they were both quite exceptionally unselfish and really fond of their fellow men.

After their honeymoon in Canada and England, including the first of her many visits to Cornwall, they settled into their new home at No. 1 West Franklin Street, Baltimore, where they started that generous dispensation of delightful hospitality which continued to the end and which was especially attuned to and treasured by the young, as I have good reason to remember. Of Osler's gifts in this direction I will only say that he was a loved father to all us boys, but surely no one ever possessed in fuller measure the capacity to make young people feel at home and wanted than Grace Osler.

The frequent absences necessitated by William's work and attendance at meetings never interfered with the closeness of their attachment and probably increased the pleasure of their holidays, especially their times at sea, free from interruptions.

In February 1893 a son was born to them, but lived only a few days. Fortunately, however, another son was born on December 28, 1895, and was christened Edward Revere. The advent of this baby was not, however, allowed to interfere with Grace's numerous social activities in Baltimore and Maryland generally, in which the training and welfare of nurses occupied a prominent position.

During the next few years her husband's responsibilities and the demands made upon him from every side steadily increased and Grace became anxious for his health. So the offer of the Regius Chair at Oxford was greeted by her with profound thankfulness and she urged him to accept it, in spite of the awful wrench she knew it would involve. She it was who organized with faultless efficiency the move from Franklin Street and the disposal of their surplus possessions and on May 27, 1905, they arrived at 7 Norham Gardens, Oxford, which they had taken furnished from Mrs. Max-Müller. She loved the new life in Oxford, and their immediate popularity was a rare tribute from a rather reserved society. I have no space to give here Grace's amusing descriptions of her experiences and reactions, with which she often entertained her friends in later years. Soon they moved into their final home at 13 Norham Gardens, affectionately nick-named "The Open Arms", whose magic atmosphere of culture, bustle and fun I so well remember. On King George V's accession Mrs. Osler was presented at Court and in the Coronation Honours William was made a baronet.

On July 31, 1914, Grace and their son Revere embarked for Canada and they were still at sea when the War began, so back they came by the same boat and Grace immediately became immersed in war work with all her usual enthusiasm and efficiency. When in August 1917 Revere was killed, serving with his battery in France, her thought was all for William, who, in spite of the courageous face he showed the world never really recovered from the blow, and a long cold motor journey from Newcastle in September 1919 started the illness from which he died in December of that year.

How, after these two terrible blows, she managed to carry on the tradition of "The Open Arms", at the same time helping Harvey Cushing with her husband's biography and others with the completion of the Osler catalogue, in preparation for the transfer of the precious books, the chief pride and ornament of their home, to McGill University, in accordance with his last wishes, will always seem miraculous to anyone who can form a conception of what this involved. On December 23, 1927, she had a slight stroke, from which she did not recover until the following March, and she just hated this unaccustomed illness, but it was not until August 31, 1928, when this tremendous task was just completed and the first boxes destined to take the books to Canada had just arrived, that Grace Revere Osler died quietly in her home.

MARY ELIZABETH BRUCE

In writing an account of Lady Bruce and her work, I have the special satisfaction of knowing that I am fulfilling her husband's dying wish that in any notice which might be made of his scientific work there might be included a statement of how much he had been indebted to her expert help.

Mary Elizabeth Steele was born in 1849 and was the daughter of John Sisson Steele (1809–1889), the predecessor in the Reigate practice of Dr. Stone, to whom David Bruce became an assistant in 1881. In 1883 David, who had recently obtained a commission in the Army Medical Service, passing out first in the list from the old Army Medical College at Netley, married Mary, and so began a beautiful life-long partnership in which, alone of all the marriages with which I am dealing in this Address, the wife made important and often vital scientific contributions to her husband's work. In 1884 David Bruce was posted to Malta, when he at once recognized the importance of "Malta fever", now known as "undulant fever" or "brucellosis", with cases of which the Naval and Military hospitals were filled. But it was, apparently, because he was "stimulated thereto by the importunities of his wife", as Eyre puts it, that he embarked on his famous investigation of the cause of this disease, and it was with her invaluable assistance on the microscopic side that he discovered the causative organism and eventually in July 1887 grew it from the spleen of a fatal case removed aseptically ten minutes after death. Shortly afterwards the remaining Koch's postulates were fulfilled and Mrs. Bruce was able to rejoice in his triumph, in which she had played an important but, as usual, unobtrusive part.

In 1889, the Bruces left Malta and spent his leave in Berlin, where they both studied for a time in Koch's laboratory, where Mrs. Bruce perfected herself in the art of making the culture media then employed and in the technique of staining and microscopy, to such effect that with time she became an eminent microscopist and on December 16, 1931, was elected an Honorary Fellow of the Royal Microscopical Society.

This, however, was far in the future. When at the end of David's leave he was appointed Assistant Professor of Pathology at the Army Medical School at Netley, Mary was allowed to assist him in the laboratories. In 1894 he was sent to South Africa on field service and was quartered with the garrison in Pietermaritzburg, Natal. On August 4, 1895, he was promoted Major. At this time the tsetse fly was devastating the herds of natives and settlers in Natal and on the advice of Sir Walter Hely-Hutchinson, the Governor of the Colony who had been Lieutenant Governor of Malta at the time Bruce had discovered the cause of "Malta fever", Bruce was seconded from military duties to investigate the causation of this animal plague and within two

FIG. 5.—Mary Elizabeth Bruce. Reproduced from the *British Medical Journal* by kind permission.

months he had discovered *Trypanosoma brucei* and proved that nagana and tsetse fly disease were caused by the presence of this parasite in the blood. Again Mary had played an important part in this discovery, and in December 1896 she returned with him to Zululand to live for two years in a camp in the wild and isolated bush, in daub and wattle huts, subsisting chiefly on the wild game which they shot themselves, and the roughest of food and, except for the occasional visits of the English magistrate, separated from the nearest white settlers by sixty miles of wild bush. In these two years she was his only assistant and they worked out together the main facts as they are now known concerning trypanosomiasis in domestic and wild animals and the tsetse fly which transmits the organism.

In the South African War the Bruces were shut up in Ladysmith, where Bruce was in command of a large military hospital and acted as operating surgeon, whilst his wife was sister-

in-charge of the operating theatre. For her nursing work she was afterwards awarded the Royal Red Cross.

In 1901 the Bruces returned to England, but in February 1903 he was seconded by the War Office, at the request of the Royal Society (of which he had been elected a Fellow in 1899) to head the commission investigating a serious outbreak of sleeping sickness in Uganda. Again he had the invaluable assistance of his wife and by August of the same year, when they returned to England, he had proved that sleeping sickness was a trypanosome disease conveyed by the tsetse fly and that it could be transmitted from sick to healthy individuals by the bite of the fly.

In 1904 they returned to Malta where Bruce was Chairman of the Royal Society's famous Mediterranean Fever Commission, which showed that undulant fever in the island was conveyed by goat's milk.

In 1908 and again in 1911 they worked on trypanosomiasis in Uganda and Nyasaland. In the First World War they did important work together on the ætiology and control of trench fever and tetanus, for her part in which Lady Bruce was awarded the O.B.E.

In 1919 David Bruce retired and henceforth they spent the winters in Madeira for the sake of his health. She died at Artillery Mansions, Westminster, on Monday, November 23, 1931, after a long and distressing illness, and four days later David died also. Thus ended this wonderful partnership of nearly fifty years, during which they were never apart. Despite the great share she had had in his work Lady Bruce was so modest that even her intimate friends never heard her allude to her own share in his work.

So ends my little tale of noble ladies
Who helped their husbands' genius to bloom
Defying Fortune, who we know a jade is
Weaving a golden thread throughout the loom.
And though it is the past we have been scanning
Our guardian angels of to-day we know
With selfless love continually are planning
The golden harvest of the seeds we sow.

SOURCES

MARGARET CLEMENT

Dictionary of National Biography (1887) London; **9,** 33.

MACNALTY, A. S. (1959) Shakespeare and Sir Thomas More. *Reprinted from* Essays and Studies. London.

ELIZABETH HARVEY

MACNALTY, A. S. (1957) *Roy. Soc. Hlth J.*, **77,** 324.

MALLOCH, T. A. (1929) William Harvey. New York.

POWER, D'A. (1897) William Harvey. (Masters of Medicine series.) London.

ANNE HUNTER

Dictionary of National Biography (1891) London; **28,** 284.

GRAY, E. A. (1952) Portrait of a Surgeon. London.

PAGET, S. (1897) John Hunter. (Masters of Medicine series.) London.

PEACHEY, G. C. (1924) A Memoir of William and John Hunter. Plymouth.

AGNES LISTER

GODLEE, R. J. (1924) Lord Lister. 3rd ed. Oxford.

GRACE REVERE OSLER

MUIRHEAD, A. (1931) Grace Revere Osler, a Brief Memoir. Oxford.

MARY ELIZABETH BRUCE

Dictionary of National Biography, 1931–40 (1949) London; p. 108.

EYRE, J. W. H. (1936) *J. State Med.*, **44,** 64.

Lancet (1931) ii, 1201 (Obituary, Lady Bruce).

Obit. Not. roy. Soc. (1932) **1,** 79 (Obituary, Sir David Bruce).

Trans. R. Soc. trop. Med. Hyg. (1932) **25,** 305 (Obituary, Sir David Bruce).

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Meeting
April 24, 1959

Treatment of Female Genital Tuberculosis [*Summary*]

By Professor GEORGE SCHAEFER, M.D., F.A.C.S., F.A.C.O.G., F.I.C.S.
New York

CHANGING concepts in the treatment of pulmonary and extrapulmonary tuberculosis since the advent of antimicrobial therapy and resectional surgery about twelve years ago have prompted us to re-evaluate our treatment of female genital tuberculosis in the light of our present knowledge.

To plan effective treatment, the points raised by the following questions must be considered: (1) Are active extragenital tuberculous lesions present? (2) What is the extent of tuberculosis in the pelvis? (3) Will antimicrobial therapy cure pelvic tuberculosis? (4) In what type of case will surgery be necessary? (5) Is normal, full-term pregnancy possible after treatment for pelvic tuberculosis?

(1) *Are Active Extragenital Tuberculous Lesions Present?*

After a diagnosis of pelvic tuberculosis has been established, the patient must be further investigated for extragenital foci.

As a rule, active extragenital foci of tuberculosis are rarely present when the genital lesion is discovered, partly because of the natural history of genital tuberculosis, which usually has its onset five to ten years before it first comes to the attention of the gynæcologist. During the intervening period, the initial lesion in the lung usually has become arrested.

An important starting point in treatment is to determine the sensitivity of the tubercle bacilli involved to the various drugs. This can readily be done if the organisms have been bacteriologically identified, thus making them available for sensitivity studies.

Regimens of tuberculosis chemotherapy.—For patients with advanced pelvic tuberculosis, I usually use the following regimen: Isoniazid, 300 mg. daily, orally, in 2 or 3 divided doses; streptomycin, 1 gram daily, intramuscularly, for three to four weeks and then 1 gram twice a week; and 12 grams PAS daily, orally, in 3 or 4 divided doses. This regimen is continued until operation and restored thereafter. If intolerance to PAS is encountered, it is discontinued for several days and then administered in smaller doses. At times 100 mg. of pyridoxine given concurrently prevents intolerance to PAS as well as to isoniazid.

For patients with minimal disease in whom long-term therapy alone is contemplated, I use the following regimen: Isoniazid, 300 mg. daily, orally; plus 12 grams PAS orally for several years. At six months and again at twelve months the endometrial curettings and secretions are examined bacteriologically and microscopically. If these are negative, a Rubin test or a hysterosalpingogram is done following the next menstrual period. If the tubes are patent, there is some hope for conception, although mere patency is no proof of normal function. At present I am continuing such patients on antimicrobial therapy for two to three years and repeating bacteriologic and microscopic examination every four to six months. If recurrence is noted or tubo-ovarian masses appear during the course of therapy, streptomycin 1 gram twice a week is added to the isoniazid and PAS for a period of three months, and the patient is subjected to laparotomy. The extent of the procedure is determined by the findings at operation.

One difficulty we have encountered in the past with long-term streptomycin therapy is that the patients object to the injections because of pain, expense, or inconvenience. As a result they sometimes neglect to take the drug for weeks.

In patients with minimal tuberculosis treated with long-term therapy, I have frequently discontinued PAS or streptomycin after eighteen months or two years and kept the patient on isoniazid alone.

(2) *What is the Extent of Tuberculosis in the Pelvis?*

There are several varieties of pelvic tuberculosis, not only with respect to the anatomic

sites involved but also with respect to the dynamic status of the pathologic processes. It would be of great value to know the extent of inflammation, caseation, and necrosis in the pelvic viscera, and to what extent reparative processes are present.

Some years ago I presented a simple classification based on clinical evaluation of involvement of the pelvic viscera as determined by bimanual examination (Schaefer, 1955). Comparison of our clinical findings with pathologic specimens removed at operation has confirmed the value of this classification. Two types of pelvic tuberculosis are differentiated.

(*a*) Minimal pelvic tuberculosis is usually symptomless (except for sterility) and pelvic examination fails to reveal evidence of tubal enlargement or tubo-ovarian masses. The disease is discovered by bacteriologic or microscopic examination of the endometrium or from bacteriologic examination of uterine secretions. This type of pelvic tuberculosis has also been described as "latent" or "unsuspected". I would emphasize that even though enlargement of the tubes cannot be palpated, they are involved in the tuberculous process and this involvement is practically always bilateral.

(*b*) In advanced pelvic tuberculosis, palpable masses are present in the adnexa, and bacteriologic or microscopic examination of uterine secretions and endometrium reveals tuberculosis. These masses are presumed to be tuberculous, although at times they may be secondarily infected with colon bacilli, streptococci, or gonococci. Some patients will give a history of having been treated for pelvic inflammatory disease with antibiotic drugs without resolution of the symptoms or masses. This failure to respond to adequate antibiotic therapy should arouse the suspicion that the pelvic condition may be of a tuberculous nature.

Chills, fever, tenderness, or pain in the lower abdomen may be signs of an acute exacerbation or of secondary infection in pelvic tuberculosis. Nontuberculous lesions will, as a rule, respond to antibiotic therapy with a subsidence of symptoms within a week or so; an acute exacerbation of tuberculosis in the pelvis will not respond to these antibiotics.

There undoubtedly is an intermediate stage between minimal and advanced disease. This may be manifest by induration and thickening in the tubes, but this cannot be determined with certainty by bimanual examination alone.

This estimate of the extent of tuberculous involvement in the pelvis is necessary before a plan of treatment can be selected.

(3) *Will Antimicrobial Therapy Cure Pelvic Tuberculosis?*

For many years I have insisted that the same principles which govern antimicrobial therapy elsewhere in the body apply to the treatment of genital tuberculosis. The Committee on Therapy of the American Trudeau Society (1957) has recently concurred in this view and has stated, "The drug regimens and duration of therapy that are satisfactory for pulmonary and renal lesions should also be used in the treatment of female genital tuberculosis". Unfortunately, papers reporting the use of short-term antituberculosis therapy for female genital tuberculosis are still appearing in the literature. For example, in an average of 22% of 357 cases collected from the literature, endometrial tuberculosis recurred within three years after short-term therapy. Even in those patients whose endometria were apparently healed the condition of the coexistent tuberculous salpingitis cannot be determined.

Treatment of advanced pelvic tuberculosis.—On the basis of the above findings in pulmonary and renal tuberculosis, and the results of short-term therapy on tubal lesions reported from the literature, it has been our policy to give patients with advanced pelvic tuberculosis a course of antituberculosis drugs for three to four months, and if tubo-ovarian masses are still present at the end of this time, to subject them to surgery. Depending on the lesions found at operation, antimicrobial therapy is continued for at least one year post-operatively and more often for two years or longer.

Treatment of minimal pelvic tuberculosis.—The evaluation of antimicrobial therapy for tubal lesions presents a difficult problem which can be solved only through pathologic examination of the surgically removed tubes. In order to determine the results of antimicrobial therapy on the tubes as well as to arrive at the optimal duration of therapy, I have treated patients with minimal tuberculosis for varying periods from six months to three years before removing the fallopian tubes.

(4) *In What Type of Case will Surgery be Necessary?*

Because of the hazard of leaving residual necrotic foci in the pelvis, and because one cannot be certain that these have been rendered

completely innocuous by chemotherapy, I believe surgery is indicated in patients with advanced pelvic tuberculosis when the pelvic masses present at the onset of therapy still remain following a three to four months' treatment with antimicrobials. It is recognized that these masses may decrease somewhat in size in the first six to eight weeks of therapy, but if they do not disappear, one must assume that foci of tuberculosis are still present.

Surgery is also recommended in minimal tuberculosis when bacteriologic or microscopic examination reveals persistence or recurrence of tuberculous endometritis or tubercle bacilli in menstrual blood after the patient has received antimicrobial therapy for at least one year.

Following surgery, antimicrobial therapy should be given for at least one year if all foci have been removed. If there is any doubt as to whether these have been removed, antimicrobial therapy should be given for two years or more.

Radical or conservative surgery.—Bilateral salpingectomy is the minimal procedure that should be performed in the presence of tuberculous salpingitis. The greatest difference of opinion exists as to whether the uterus and ovaries should be removed in addition to the tubes. In advanced pelvic tuberculosis in which tubo-ovarian masses are present at the time of operation, the procedure which offers the patient the best chance of permanent cure is total hysterectomy and bilateral salpingectomy.

The foregoing should not be taken to indicate that I advocate total hysterectomy and bilateral salpingo-oophorectomy for all patients with genital tuberculosis. If repeated microscopic and bacteriologic examinations of uterine contents reveal no evidence of tuberculosis, and if at operation in a young woman only the tubes are involved and the uterus and ovaries appear normal, conservative surgery can be carried out.

While differences of opinion exist as to whether surgery is necessary in pelvic tuberculosis, there is agreement on the following points: (1) There is no valid reason to perform surgery in a woman known to have genital tuberculosis without a preoperative course of antituberculosis drugs. (2) Antituberculosis drugs should be given postoperatively for twelve months or more. (3) Preoperative antimicrobial therapy makes the surgical procedure simpler and reduces the risk of operative and post-operative complications. (4) Cure of pelvic tuberculosis is achieved more quickly with surgery than with antimicrobial drugs alone.

Treatment of tuberculosis diagnosed at operation.—When extensive genital tuberculosis is first discovered at the operating table, a bilateral salpingo-oophorectomy and hysterectomy should be performed. If this procedure cannot be carried out because of technical difficulties, the abdomen should be closed without drainage and a course of antituberculosis drugs given for three to four months. During this time a search for extragenital foci of tuberculosis should be made. Repeated pelvic examination will usually show sufficient regression of the disease to enable operative removal of the diseased organs at this time. Post-operative antimicrobial therapy should be given for at least one year.

(5) *Is Pregnancy Possible After Genital Tuberculosis?*

Several authors have reported that an occasional patient with proven genital tuberculosis has become pregnant. It is doubtful whether an ectopic pregnancy or an intrauterine pregnancy that terminates in early abortion and frequently leads to an acute exacerbation of the pelvic infection can be considered a good result (Studdiford, 1955).

During the past few years several reports have appeared concerning patients with pulmonary infections that, while simulating tuberculosis clinically and roentgenographically, were in fact associated with mycobacteria that could not be identified as either human or bovine tubercle bacilli (Feldman, 1959).

It appears probable to me that many cases are incorrectly diagnosed as pelvic tuberculosis solely on the basis of culture of mycobacteria from menstrual blood or from uterine secretions and without confirmation by guinea-pig inoculation. It is my opinion that this error in diagnosis is responsible for a number of published reports of pregnancies following the treatment of alleged pelvic tuberculosis.

Summary and Conclusions

I have discussed the present status of the treatment of female genital tuberculosis in the light of our knowledge of the current antituberculosis drugs and the pathologic changes found in the genital organs. A thorough evaluation of each individual patient is essential before outlining a course of therapy. It is important to remember that this course is not rigid and may be altered at any time. Several regimens of multiple drug, continual long-term therapy have been outlined. The rationale for treating minimal and advanced pelvic tuberculosis has been discussed. At the

present time I believe that the best treatment for advanced pelvic tuberculosis is pre-operative antimicrobial therapy, surgery three to four months after the onset of treatment, and post-operative antituberculosis drugs for one year or more. For minimal pelvic tuberculosis, prolonged long-term antimicrobial therapy with continual surveillance is recommended. These regimens will produce a cure of pelvic tuberculosis in almost all instances. There is practically no possibility of full-term pregnancy in a patient with advanced pelvic tuberculosis after therapy. The possibility of a normal pregnancy in patients with early, minimal tuberculosis has been discussed. It is my belief that extrauterine pregnancy will occur more frequently in this latter group than with normal full-term delivery.

REFERENCES

American Trudeau Society Committee on Therapy (1957) *Amer. Rev. Tuberc. Pul. Dis.*, **75,** 524.
FELDMAN, W. (1959) Personal communication.
SCHAEFER, G. (1955) *Amer. J. Obstet. Gynec.*, **69,** 1333.
STUDDIFORD, W. E. (1955) *Amer. J. Obstet. Gynec.*, **69,** 379.

The following specimens were shown:

Uterocolic Fistula.—Mr. E. R. PARRY.

Vaginal Atresia of Arabia (Four cases).—Miss KATHLEEN FRITH.

Massive Venous Occlusion with Gangrene of Foot Following Colporrhaphy. — Miss VALERIE THOMPSON.

Meeting
May 22, 1959

Subarachnoid Hæmorrhage in Pregnancy

By D. E. CANNELL, M.B., F.R.C.S.(C.)
Toronto, Canada

IN 1956 Cannell and Botterell reported the results of treatment in 16 cases of subarachnoid hæmorrhage which occurred during pregnancy. In the interval, a further 10 patients have been studied with the same complication. The significance of this condition as a factor in maternal mortality is emphasized by the decrease in deaths of obstetric ætiology and the fact that 50% of such patients will die within eight weeks if untreated. Our opportunity to study this problem is unique as the Neurosurgical Service at the Toronto General Hospital attracts difficult problems from a large area of the Province of Ontario with a population in the neighbourhood of six million people.

Material (Table I).—In 4 of the 16 patients reported by us in 1956, the subarachnoid hæmorrhage was associated with other complications of pregnancy. In this further study, 1 patient was pre-eclamptic. This leaves a total of 21 patients in whom the pregnancies were otherwise normal and these form the basis for consideration.

TABLE I.—SUBARACHNOID HÆMORRHAGE AND PREGNANCY

Spontaneous hæmorrhage		21
Aneurysm	12	
Arteriovenous malformation ..	4	
Undetermined	5	
Secondary hæmorrhage		5
Pre-eclampsia	3	
Sinus thrombosis	1	
Mycotic aneurysm (subacute bacterial endocarditis) ..	1	

Diagnosis.—Severe headache, frequently occipital in distribution, nuchal rigidity, nausea and vomiting, hemiplegia and involvement of the cranial nerves occurred in this order of frequency. A grossly bloody or xanthochromic spinal tap was noted in all patients. Confirmation of the diagnosis was obtained by angiogram in the majority of cases. Difficulty in differentiating this lesion from pre-eclampsia occasioned concern initially. Our recent experience suggests that it is a greater hazard to life if the pre-eclamptic is suspected of and treated as a spontaneous subarachnoid hæmorrhage.

Incidence.—We are in agreement with Walton (1952) that subarachnoid hæmorrhage in pregnancy does not differ from that in the general population. Our incidence is about 1 in 2,000 pregnancies. This is probably fallacious and reflects the interest shown in the management of abnormalities of intracranial blood vessels by our neurosurgical colleagues.

Time of occurrence.—There were 22 primary subarachnoid hæmorrhages in these 21 patients, 1 of whom had a subarachnoid hæmorrhage in two pregnancies (Table II).

Subarachnoid hæmorrhage occurred almost equally between the first and second half of pregnancy: 9 in the first 20 weeks and 13 in the last 20 weeks or the early puerperium. None occurred during labour though the effect of labour on the 2 occurring early in the puerperium cannot be discounted.

TABLE II.—TIME OF OCCURRENCE OF 22 PRIMARY SUBARACHNOID HÆMORRHAGES

1 at 6 weeks	2 at 24 weeks
1 at 10 weeks	1 at 26 weeks
2 at 16 weeks	2 at 28 weeks
2 at 18 weeks	1 at 33 weeks
4 at 20 weeks	1 at 37 weeks
2 at 22 weeks	1 at 40 weeks

Postpartum:
1 at 2 hours after delivery
1 at 4 hours after delivery

Total 22

Source of spontaneous subarachnoid hæmorrhage in pregnancy (Table III).—In 12, the subarachnoid hæmorrhage arose from intracranial aneurysms, 4 from arteriovenous malformation and in 5 the source of hæmorrhage was undetermined. Subsequent arteriography or autopsy reveals that ruptured aneurysms are the source of hæmorrhage in a significant number of those of undetermined origin.

TABLE III.—SPONTANEOUS SUBARACHNOID HÆMORRHAGE IN PREGNANCY

	Mortality
12 aneurysms	3
9 others	0

Management.—In our earlier report we suggested that: (1) The management of subarachnoid hæmorrhage in pregnancy should not differ from that in the non-pregnant state; (2) The obstetrical management should be conservative, Cæsarean section being performed on indication rather than by election; (3) Pregnancy does not influence the incidence or outcome; (4) The selection of anæsthetic method is of great importance if surgery is performed during pregnancy.

We are aware that it is difficult to draw firm conclusions from such a small series. We feel justified, however, in presenting our findings and observations as they represent a relatively large experience in a single institution.

In this respect we found that 16 lesions were localized radiologically; 9 were treated surgically with 1 death; 7 were treated conservatively with 2 deaths. This suggests that where the lesion is localized and amenable to surgical treatment, the results of operation justify the procedure.

Obstetric management.—In these 21 patients, 14 were delivered vaginally, 5 by Cæsarean section, and 2 died undelivered. We feel that all patients treated by neurosurgery may be delivered vaginally, Cæsarean section being reserved for obstetrical indications. Skilful assistance in the second stage should eliminate any danger from rupture of aneurysms due to elevation of blood pressure during the course of delivery. In the group managed medically, we feel that there is little risk to labour and delivery by the vaginal route that is not present in Cæsarean section.

Pregnancy and subarachnoid hæmorrhage.—If Walton's findings are accepted that the occurrence of subarachnoid hæmorrhage is no more frequent in the pregnant than nonpregnant population, what effect has pregnancy upon the outcome of this condition? We have reviewed some 80 females admitted to the Toronto General Hospital with proven subarachnoid hæmorrhage (Table IV).

TABLE IV.—SUBARACHNOID HÆMORRHAGE IN FEMALES

		Mortality
80 *Cases*		21
5 Secondary		4
75 Spontaneous		17
8 Prior to pregnancy ..	0	
21 During pregnancy	3	
25 After pregnancy	7	
21 Never pregnant	7	

It can be seen from this that, apart from those in whom the subarachnoid hæmorrhage was secondary to other complications of pregnancy, the mortality is not significantly altered in those in whom the accident occurred during pregnancy as opposed to those occurring after pregnancy or where the women have never been pregnant. Indeed, in the small group who were never pregnant, the mortality was greater than that in any other classification. The 8 patients who became pregnant subsequent to subarachnoid hæmorrhage had 6 full-term deliveries and 3 therapeutic terminations of pregnancy. 2 of the latter were performed for equivocal reasons.

Anæsthesia.—Hypotensive anæsthesia has proved to be a valuable adjunct in the surgical management of intracranial aneurysms. Systemic hypothermia has been employed in our centre for the same purpose. Hypotensive anæsthesia was used in 2 pregnant women, 1 at 18 weeks and 1 at 33 weeks. Both infants survived and showed no evidence of cerebral damage from anoxia. We feel, however, that this form of anæsthesia carried too great a theoretical hazard to the fœtus. After a study carried out on experimental animals, we are satisfied that hypothermia is a safer form of anæsthesia for the fœtus. We have accordingly begun to use it as the anæsthetic of choice where surgical attack upon intracranial lesions in pregnant women is attempted. To date, encouraged by our experimental work, 1 pregnant patient has been successfully treated, with the survival of a normal healthy infant.

Summary.—Valid and final conclusions are difficult to arrive at from such small numbers. We see, however, no reason to alter the view expressed in 1956 that:

(1) Subarachnoid hæmorrhage in pregnancy is not as rare as has been reported previously.

(2) Subarachnoid hæmorrhage complicating a *normal* pregnancy requires prompt neurologic and angiographic investigation.

(3) Prompt surgical treatment is indicated as definitely in the pregnant as in the nonpregnant patient.

(4) The obstetrical management of such patients should be based upon sound principles, Cæsarean section being employed where indicated and not routinely.

REFERENCES

CANNELL, D. E., and BOTTERELL, E. H. (1956) *Amer. J. Obstet. Gynec.*, **72,** 844.
WALTON, J. N. (1952) *Brit. med. J.*, ii, 802.

DISCUSSION ON TREATMENT OF CONGENITAL ABSENCE OF VAGINA WITH EMPHASIS ON LONG-TERM RESULTS [*Abridged*]

Sir Archibald McIndoe (London):

The operation described by the author in 1938 seems to have established itself as the standard method when judged by the requirements of ease of performance, low morbidity, no mortality and excellent end-result (McIndoe and Banister, 1938). This operation has now been carried out on 105 patients during the past twenty-two years and it has naturally passed through various modifications in that time. 103 of the patients operated upon suffered from congenital atresia of varying degree, while the remaining two were treated for strictures acquired in later life.

Until 1938 there was no settled opinion as to the correct management of vaginal atresia. Five methods were generally used:

(1) Intestinal transplantation (Baldwin, 1904; Mori, 1910; Popoff, 1910; Schubert, 1911).

(2) Pedunculated flaps (Graves, 1921; Frank and Geist, 1927).

(3) Simple pressure (Frank, 1932).

(4) Simple reconstruction, mostly grafts (Kanter, 1935; Wells, 1935; Wharton, 1946; Counseller, 1948).

(5) Free grafts (Heppner, 1872; Abbe, 1898; Pickerill, 1924; Kirschner and Wagner, 1930; Meyer, 1935; Monod and Iselin, 1936; McIndoe, and Banister, 1938; McIndoe, 1950).

Inlay grafting was developed from Esser's epithelial graft (1917) and modified by Gillies for the eye socket, the oral and nasal cavities (1920) and by McIndoe for the external auditory meatus, and the urethra (1937*a*, *b*, *c*).

The principles of inlay grafting are: (*a*) Careful preparation of the cavity. (*b*) Complete hæmostasis and asepsis. (*c*) Thin split skin graft in one piece. (*d*) Continuous (not intermittent) dilatation until the contractile phase is overcome.

Description of the operation and after-care.—A cavity is prepared between the rectum and urethra in the loose areolar tissue between the two structures and enlarged upwards to the pouch of Douglas by finger dissection. It is made sufficiently big to accommodate a mould exactly the same size as that carrying the graft. After hæmostasis the light, hollow, graft-covered mould is inserted into the cavity and a perineal bridge built beneath it so that it cannot slip out. The urethra is not obstructed but, for the first few days, a self-retaining catheter is worn. The mould is left in place for four months and then removed. A polythene dilator is used continuously for at least six months and only discarded when all tendency to contraction has ceased. (For further details *see* Berkeley and Bonney, 1942.)

The end-results were as follows:

Vagina measures 12 × 3 cm.—excellent result ..	89%
Vagina measures 7 to 12 × 3 cm.—satisfactory result	6%
Vagina measures less than 7 cm.—poor result .. (mould discharged or removed too early with complete contraction—failure)	5%

Summary.—Utilizing modern plastic principles of inlay grafting and continuous dilatation until the contractile phase is over it is possible to construct an entirely satisfactory vagina with a high percentage of success (89%) and a low rate of failure (5%) without danger to life and with low morbidity. From the gynæcological standpoint the functional effect can be obtained by no other procedure.

REFERENCES

ABBE, R. (1898) *Med. Rec.*, **64,** 836.
BALDWIN, A. F. (1904) *Ann. Surg.*, **40,** 398.
BERKELEY, C., and BONNEY, V. (1942) Textbook of Gynæcological Surgery. 4th ed. London, etc.; Chapter VII.
COUNSELLER, V. S. (1948) *J. Amer. med. Ass.*, **136,** 861.
ESSER, J. F. (1917) *Ann. Surg.*, **65,** 307.
FRANK, R. T. (1932) *Amer. J. Obstet. Gynec.*, **33,** 256.
——, and GEIST, S. H. (1927) *Amer. J. Obstet. Gynec.*, **14,** 712.
GILLIES, H. D. (1920) *Surg. Gynec. Obstet.*, **30,** 121.
GRAVES, W. P. (1921) *Surg. Clin. N. Amer.*, **1,** 611.
HEPPNER (1872) Cited by A. Paunz (1923) *Zbl. Gynäk.*, **47,** 883.
KANTER, A. E. (1935) *Amer. J. Surg.*, **30,** 314.
KIRSCHNER, M., and WAGNER, G. A. (1930) *Zbl. Gynäk.*, **54,** 2960.
MCINDOE, A. H. (1937*a*) *Surgery*, **1,** 535.
—— (1937*b*) *Brit. med. J.*, i, 385.
—— (1937*c*) *Amer. J. Surg.*, **38,** 176.
—— (1950) *Brit. J. plast. Surg.*, **2,** 254.
—— and BANISTER, J. B. (1938) *J. Obstet. Gynæc. Brit. Emp.*, **45,** 490.
MEYER, F. M. (1935) *Dtsch. Z. Chir.*, **244,** 379.
MONOD, R., and ISELIN, M. (1936) *Mém. Acad. Chir.*, **62,** 997.
MORI, M. (1910) *Zbl. Gynäk.*, **34,** 11.
PICKERILL, H. P. (1924) Facial Surgery. Edinburgh.
POPOFF, D. D. (1910) *Russk. Vrach.*, **60,** 1512.
SCHUBERT, G. (1911) *Zbl. Gynäk.*, **35,** 1017.
WELLS, W. F. (1935) *Amer. J. Surg.*, **29,** 253.
WHARTON, L. R. (1946) *Amer. J. Obstet. Gynec.*, **51,** 866.

Mr. Clifford A. Simmons (London):

Vaginoplasties at Chelsea Hospital for Women 1938–1958

There have been 101 McIndoe vaginoplasties at Chelsea Hospital for Women between the years 1938 to 1958. Some were performed earlier and have not been included in this series. The majority of patients were operated upon by Sir Archibald McIndoe and Sir Charles Read, and therefore this series overlaps Sir Archibald's personal series, but all other members of the staff have performed this operation and 9 personal cases are included.

The type of patient.—The different types of patient are shown in Table I. 85 patients had

TABLE I.—VAGINOPLASTIES AT CHELSEA HOSPITAL FOR WOMEN

Type of Patient	No.
Congenital absence of vagina	85
Pseudohermaphrodites	5
Atresia of the vagina or congenital absence of some portion causing hæmatometria ..	5
Acquired vaginal stenosis	6

Age 57, following a repair.
Age 57, vaginoplasty three years previously.
Age 43, following vaginal hysterectomy.
Age 26, following vaginal lacerations.
Age 18, following subtotal hysterectomy for postpartum hæmorrhage.
Age 18, following delivery and repair of fistula-in-ano.

congenital absence of the vagina, which was represented in the majority by a small dimple. The adnexa had been palpated in some cases under an anæsthetic and often the uterus was represented by a small nubbin of tissue in the mid-line. These patients were usually quite attractive and feminine in appearance, often being slight in build with an "elfish" look. Congenital absence of some portion of the vagina occurred in 5 patients resulting in hæmatometria. One patient also had a double uterus.

There were 5 pseudohermaphrodites. 3 of these had had testicular tissue removed at the time of laparotomy or herniorrhaphy. One suffered from adrenal-cortical hyperplasia.

6 patients had acquired stenosis (Table I).

TABLE II.—AGE AT OPERATION
Patients with Congenital Absence or Atresia of the Vagina

Ages	No.
15–20 years	33
21–25 years	36
26–30 years	19
31–35 years	4
36–46 years	3
Total	95

The age at operation.—The age groups are shown in Tables I and II. The majority were 19 to 24 years of age, but some were much older.

Marital status.—36 patients were married at the time of the operation. Usually the operation was postponed until the wedding had been arranged, but of the patients with congenital absence of the vagina, one had been married for four years, one for six years, two for eight years and one for fifteen years.

Complications (Table III).—The commonest

TABLE III.—THE COMPLICATIONS OF OPERATION (101 vaginoplasties)

Early extrusion of the mould requiring resuture	19
Urinary infections	13
Urethrovaginal fistula	1
Rectovaginal fistulæ	4
Hæmorrhage	2
Deep calf-vein thrombosis	1
Keloid of the skin donor area	1

complication was early extrusion of the mould and in 19 cases the mould had to be replaced and the perineum re-sutured. All the patients who eventually had an unsatisfactory result from operation had had early extrusion of the mould. The mould was usually left *in situ* for four and a half to five months. If the mould is extruded early, the vagina quickly shrinks down and it may be impossible to replace the mould even in twenty-four hours' time. If the mould is extruded late, daily vaginal dilators may be sufficient.

Severe urinary infections occurred in 13 patients; these were all controlled by sulpha drugs or antibiotics. An indwelling catheter was left for eight to ten days and normal voiding of urine usually occurred after that time. One patient, however, developed retention of urine when the catheter came out early and a temporary suprapubic cystostomy was made. One patient complained of stress incontinence of urine two years after the original operation. She was found to have a small urethrovaginal fistula which was closed with a good result.

Rectal fistulæ developed in 4 patients. A small fistula was found at the vault of the vagina when the mould was removed at five months. This was treated by vaginal dilators, and the fistula healed spontaneously with a slightly shortened but adequate vagina. 3 other patients developed fistulæ at three weeks, six weeks and seven weeks after operation. The last 2 passed the mould rectally. The vagina shrank down to 1½ in. with healing of the fistulæ in these three cases.

Hæmorrhage occurred in 2 patients. One had to be transfused twenty-four hours after the operation and the mould was removed and blood clot cleared out. The mould was then replaced and the perineum re-sutured and the final result when the mould was removed after five months was very good. Another patient had a severe hæmorrhage on the eleventh day. The mould was removed and the vagina irrigated and packed. Vaginal dilators were used when the pack was removed. The final result was a functioning but shortened vagina. In both these cases the skin graft survived, and it would

seem that a graft "takes" within a very short time of operation.

The donor skin area.—One patient developed keloid in the scar, but this gradually improved and after three years the scar was only just noticeable. Another patient who had a vaginoplasty five years previously was very fond of sunbathing. She complained that when she became tanned, the donor area on the thigh remained a blotchy white. This was confirmed when she was examined and she was advised to use cosmetics on the affected area.

Deep calf-vein thrombosis.—One patient developed a deep thrombosis and made an uneventful recovery with treatment.

The fate of the graft.—The graft "takes" shortly after operation. Only on one occasion was the graft rejected completely together with the mould on the tenth day. Section of the graft showed that it was necrotic. 3 patients had a second graft applied when the mould was removed. Several patients had a small area at the vault of the vagina where the graft had not taken. These were treated by curettage of the granulations and the passage of dilators. Biopsy of the vaginal skin five months after operation at the edge of an area of granulation tissue, showed that there was normal squamous epithelium with a small ulcer at one edge of the section. It is of interest that the vaginal skin was reported to give a positive stain for glycogen. Vaginal smears have been taken from some patients and these are similar to smears taken from the lower third of the vagina of normal patients. The pH of the new vaginæ in the few patients examined varied from 6 to 8.

The results of operation.—The primary results are shown in Table IV. There were 4 failures and 3 patients who had a short vagina, but who managed successful intercourse.

TABLE IV.—THE PRIMARY RESULTS OF OPERATION (1938–1958)

Successful result	94	
Partial success	3	Short but adequate vaginæ, requiring the use of dilators. One recto-vaginal fistula which healed spontaneously
Unsuccessful	4	3 rectovaginal fistulæ 1 short vagina
Total	101	

The long-term results are shown in Table V. In the time available it has only been possible to follow up 39 patients, 2 of whom had repeat operations. Between 1948 and 1958, 60 vaginoplasties were carried out. 32 patients had an excellent result and were leading normal married lives. 3 were found to have some stenosis of the upper third of the vagina the effective length of which was 3 to 3½ in. The upper third was represented by a track that would admit the tip of the little finger. These patients are being

TABLE V.—THE LONG-TERM RESULTS OF OPERATION (1948–1958)
(60 vaginoplasties, 41 operations on 39 patients followed-up)

Time of follow-up in years	Successful	Partial success	Failures
10	4	1	1 (no intercourse)
9	2	—	1* (,, ,,)
8	1	—	—
7	1	—	—
6	1	1	1* (satisfactory 5 years)
5	6	—	1 (2½ in. vagina)
4	1	—	—
3	6	—	1 (rectovaginal fistula)
2	7	—	1 (rectovaginal fistula)
1	3	1	—
	32	3	6

*Repeat vaginoplasty.

treated with dilators. Of the failures 2 had stenosis following rectovaginal fistulæ, 2 did not have intercourse after the operation and 2 developed stenosis after a satisfactory primary result.

If regular intercourse does not take place the vagina may decrease in size. One patient, 43 at the time of operation, when examined ten years later had a vagina 3 in. long, which only admitted one finger. Another patient had a vaginoplasty at the age of 23 with an excellent result. She did not marry until nine years later, by which time the vagina was only 1½ in. long. She had a repeat operation. After six years of normal married life a patient developed dyspareunia and did not have intercourse for a year. The vagina when she was seen after that time was found to be only 1½ in. in length and she also had a second operation. Sir Archibald McIndoe performed a vaginoplasty on a girl of 17 in 1943. She was examined four years later and found to have a perfect result. Previously she had had a laparotomy and the uterus was found to consist of a small mass of tissue only. In 1957 when she wished to marry the vagina was only 2½ in. long and she had developed two large fibroids in the rudimentary uterus. She had a repeat vaginoplasty and the fibroids removed.

It is therefore necessary that patients who cannot marry after the operation, or patients who develop dyspareunia, should be seen so that they understand that they must continue passing vaginal dilators.

Acknowledgments.—My thanks are due to Sir Archibald McIndoe and the late Sir Charles Read, and to all the staff of Chelsea Hospital for Women for permission to see their patients.

Mr. Frederick W. Roques (London) showed a film illustrating the construction of an artificial vagina, following McIndoe's technique, with a report of 15 cases.

Dr. C. Seah (London) introduced a film to show Professor B. H. Sheares' technique for the treatment of congenital absence of the vagina.

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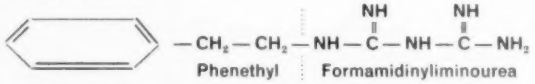

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Oral Treatment of Diabetes — Hall, Crowley and Bloom, B.M.J., July 12th, 1958, p.71

Clinical Use of the Biguanides and their Role in Stabilizing Juvenile-type Diabetes – Krall, White and Bradley, Diabetes November 1958, 7: 468.

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Section of Comparative Medicine

President—F. O. MacCallum, M.D.

Meeting
May 20, 1959

DISCUSSION ON INHERITED METABOLIC CHARACTERS IN MAN AND ANIMALS

Mr. A. L. Ogden (Stock, Essex):

Biochemical Polymorphism in Farm Animals

"The morphological characteristics of plant and animal species form the chief subject of the descriptive natural sciences and are the criteria for their classification. But not until recently has it been recognized that in living organisms, as in the realm of crystals, *chemical differences parallel the variation in structure*." This quotation from Landsteiner belongs to 1936 but it is only in the last ten years or so that interest in the heritability of biochemical variations has become acute.

This quickening owes much to the teachings of Sir Ronald Fisher, E. B. Ford and other neo-Darwinists. Their appreciation of the way in which natural selection acts upon such variants and of how the relative frequencies of the genes involved may become stabilized for a particular environment by a balance of selective pressures, has introduced new lines of enquiry into several disciplines.

For those not familiar with the sequence that has been followed by investigations of this type, a résumé may be appropriate. The first stage is the observation amongst the normal individuals of the species, of distinct variants in some particular biochemical character and the verification that such subdivision of the norm is both valid and permanent. The second is the accumulation of mating data to establish their genetic basis and mode of inheritance and the third, the calculation of the appropriate gene frequencies from representative samples of the species and the search for differences in frequency within the species based either on morphology or on environment. Finally these investigations extend to a search for clues as to the nature of the selective pressures involved in maintaining the balance of types observed. At each of these broad stages there are many possible refinements and digressions and the use to which any such inherited biochemical markers can eventually be put in the field of genetics is clearly foreshadowed by the intense activity at present centred on blood groups.

For example, Harris and Warren (1955) reported the occurrence of electrophoretically distinct hæmoglobins in ruminants, differences being demonstrated in both the goat and the sheep and a distinction being drawn between the adult variants observed and fœtal hæmoglobin. The genetic basis of this observation was reported by Evans *et al.* (1956). The former paper indicated that there were two kinds of hæmoglobin, the relatively fast sheep hæmoglobin A and the slower moving sheep hæmoglobin B, giving the three phenotypes A, B and AB. The latter paper suggested that these hæmoglobin types were determined by two alleles each responsible for the formation of one kind of hæmoglobin. Later the distribution of these hæmoglobin types in British breeds of sheep was investigated (Evans *et al.*, 1957); it then became apparent, from data based on 4,500 sheep, that lowland breeds were predominantly of hæmoglobin type B (eighteen such breeds had gene frequencies for B greater than 0·8) and that in mountain and hill breeds the situation was reversed and hæmoglobin A was predominant. Although these environmental differences in gene frequency strongly suggested that the hæmoglobin types had or might have had some adaptive significance its nature remained undetected. More recently King *et al.* (1958) examined the performance of these types in a single large flock of 1,500 Scottish Blackface ewes using criteria of reproductive ability, growth rate and fleece characteristics but failed to find any significant differences which might explain the widely varying gene frequencies observed in different breeds.

An explanation of this polymorphism was provided by Jonxis *et al.* (1958) who found a difference in the oxygen dissociation curves of the two sheep hæmoglobins. Sheep hæmoglobin A, which is the predominant type in mountain

breeds, has the greater affinity for oxygen. Natural selection has thus favoured this type at high altitudes, a selective advantage which is lost at low altitudes where the oxygen content of the atmosphere is high enough to permit the B type to compete successfully. Freed from this disadvantage the lower oxygen affinity of sheep hæmoglobin B facilitates the release of oxygen to the tissues and, in certain circumstances, the balance of advantage is reversed and the B gene predominates. It was also shown that in the heterozygote, which was able to produce both hæmoglobins, their relative proportions were adjusted according to whichever stress conditions were applied. This adaptability may well provide a precise example of the type of factors contributing to the success of the widespread cross-breeding practices on hill and upland farms; the mating of hill-bred ewes of high A gene frequency with fast maturing lowland rams of high B gene frequency ensures a high proportion of heterozygotes in the F.1 generation capable of producing either type of hæmoglobin and therefore of taking full advantage of the better lowland conditions.

Thus in the case of the sheep hæmoglobins results have been achieved in each of the investigational stages outlined. In every way it seems to provide a model for this type of study, which is the reason why I have chosen sheep hæmoglobins as my first example of biochemical polymorphism in farm animals.

Cabannes and Serain (1955) reported the detection of two types of adult hæmoglobin in Algerian hill cattle using paper electrophoresis. Differences in the distribution of these two cattle hæmoglobins have been studied by Bangham (1957). He describes them as bovine A and bovine B hæmoglobins and in this case it is the bovine B type which is the faster moving. Bangham showed that the cattle hæmoglobins were also controlled by two autosomal allelic genes fully expressed in the heterozygote. An interesting feature of cattle hæmoglobin types is that amongst the breeds common in Britain the B type is found in Jersey, Guernsey and South Devon cattle only. The cattle hæmoglobin types therefore illustrate a further use to which this type of study can be put, namely the study of the geneology of particular breeds. This was appreciated by Bangham (1958) who showed that the presence of the B gene in Southern European and African breeds of cattle was consistent with one of the suggested ancestral lines of the Jersey breed (that postulating descent from cattle of the ancient Indus valley civilization, and from thence through Africa to Europe).

In man the application of data of this type to anthropology is well appreciated. Human hæmoglobin D, for example, has been used to trace ethnic connexions between certain races; an extensive and corresponding use has been made of human blood group data: the affinity of the ABO distribution of the Central European gypsies with that of the Hindus (Verzar and Weszeczky, 1921); of the Scottish and Northern Irish blood group frequencies with the Icelandic; and of the Southern English with the Continental (Fisher and Taylor, 1940) are well known. But Bangham's observations are, so far as I am aware, the only attempt to use such data to elucidate the ancestry of individual breeds of farm livestock.

A note of caution in this type of use of biochemical markers has recently been struck by the Cambridge work on the chemical structure of the hæmoglobin molecule, for it has been shown that hæmoglobin D from three different racial sources showed distinctive small differences in the peptides yielded, suggesting three independent sources rather than a single common ethnic origin as at first assumed.

In his later paper Bangham suggested there was prima facie evidence of correlation between the absence of bovine B hæmoglobin and relatively high tolerance to trypanosomiasis. The idea that the selective pressures involved in the balance of types might be, in certain environments at least, a differential disease susceptibility illustrates a further aspect of metabolic polymorphism of great potential interest. It is supported by work on the presence of sickle cell hæmoglobin and resistance to falciparum malaria in man (Allison, 1954). In animals, however, there is obviously a great deal of groundwork still needed. Differential disease susceptibility is an aspect which I shall return to later in this paper.

In 1955 Aschaffenburg and Drewry reported the occurrence of different β-lactoglobulins in cow's milk. Individual cows produce either a mixture of two electrophoretically distinct β-lactoglobulins or only one or the other of these. A complication to the study of the genetic control of the production of these two types is the inability to assess the phenotype of males; however, the same authors were able to produce evidence that the formation of these two β-lactoglobulins was controlled by a single gene (Aschaffenburg and Drewry, 1957), the separate proteins formed under the influence of each allele being both present in the heterozygote. It is of interest that these authors consider that the

gene controlling formation of cattle lactoglobulins is probably unrelated to that responsible for their hæmoglobins and also to those controlling their serum proteins (β-globulins).

Although the significance of the different lactoglobulins is uncertain the authors make the interesting suggestion that because "milk is produced to nourish the young . . . differential effects may have to be sought in the calf that receives the milk rather than in the cow that secretes it". They observed *quantitative* differences in each of the β-lactoglobulins which were related to the casein content of the milk. These findings indicated that "given equal yields of milk of comparable casein content an animal homozygous for the Lg^A allele will produce almost twice as much β-lactoglobulin as the other homozygote, while the output of the heterozygote falls about half-way between that of the two homozygotes". They infer that this enhanced production of lactoglobulin stimulated by the Lg^A allele may be nutritionally advantageous to the calf but admit that in all the breeds tested the frequency of Lg^B is higher than that of Lg^A. Any such selective nutritional advantage to her own calf would be broken down under calf management systems involving pail feeding of mixed milks, a common modern dairy practice, but would be retained in the case of natural suckling beef breeds. The majority of animals studied by Aschaffenburg and Drewry belong to the Shorthorn, Friesian, Ayrshire and Guernsey breeds; 23 other animals are classed as miscellaneous breeds and in this group the frequency of Lg^A is the highest recorded. It seems possible that more detailed individual examination of the lactoglobulin gene frequencies of pure beef breeds might well be worth while. The possibility of differential neonatal disease susceptibilities in the recipient calves, and any possible association of change in the β-lactoglobulin type of the milk fed with the diarrhœas commonly seen in calves changing hands while very young, may well merit incidence studies.

Before passing on to the serum proteins, with which I wish to deal finally, I will make brief mention of some of the other inherited biochemical characters of farm animals that have been reported in the literature. Evans (1954) has shown that sheep fall into one of two groups on the basis of the concentrations of sodium and potassium in their red blood cells. Sodium concentration varies inversely with potassium concentration and the two types have therefore been designated simply "high potassium" (HK) and "low potassium" (LK). This dimorphism is controlled by a pair of alleles, but in this case the allele responsible for the HK phenotype behaves as a recessive. Low potassium animals are therefore of two types, those homozygous and those heterozygous for the LK allele. The genes for this factor and those for the sheep hæmoglobin types appear to segregate independently (Evans and King, 1955; Evans, 1954).

Allison and ap Rees (1957) reported on genetically controlled differences in catalase activity of dog erythrocytes, control being based on a single pair of alleles with the heterozygote's activity coming intermediate between those of the two homozygotes. These authors refer to a much earlier Russian paper, Putilin (1929) reporting high and low erythrocyte catalase-levels in cattle under similar genetic control. The explanation of these interesting polymorphisms is not known.

Other polymorphisms in enzyme activities have been reported; atropine esterase in the rabbit (Sawin and Glick, 1943) and gene-controlled esterase activity in swine (Augustinsson and Olson, 1958). It is obvious from literature on work in man that enzyme activity is a fruitful field for this type of study.

Blumberg and Tombs (1958) reported the existence of two types of α-lactalbumin, genetically controlled, in Nigerian White Fulani cattle. This is the only breed so far examined which has been found to be dimorphic for this factor.

Finally, I wish to discuss serum protein polymorphism in farm animals with particular reference to cattle, for this system illustrates a further way in which this type of study can be developed. Ashton, a former colleague of mine at the Farm Livestock Research Centre of the Animal Health Trust, adapted starch gel electrophoresis, a technique originally developed by Smithies (1955) in the definition of human haptoglobins—for use with sera of domestic animals. In Ashton's hands this technique has proved an elegant means of displaying differences in serum protein pattern. He has been able to differentiate the β-globulin components of cattle, sheep, goat and horse sera and has examined their mode of inheritance (Ashton, 1957, 1958*a*). He has also detected other inherited differences in serum protein pattern, namely, thread proteins (Ashton, 1957, 1958*b*), a newly described component probably derived from the albumin fraction, and also a difference in the slow alpha proteins in Guernsey cattle (Ashton, 1958*c*); this zone could not be found in two out of 150

Guernseys examined and this pair was daughter and dam. Of these inherited differences it is only the cattle β-globulin system I wish to discuss in more detail.

British breeds show six β-globulin phenotypes and these represent the individual homozygotes and heterozygotes of three pairs of alleles β^A, β^D and β^E. In this system the E gene is relatively rare and was absent altogether from the Jersey, Guernsey and South Devon cattle examined. In the British Isles the frequency of β^E in the Ayrshire breed at least, appears to increase as one goes northwards. Ford and others have explained how differential fertility levels will parallel the success or lack of success of types within a polymorphic system. This may be dependent upon differences in general viability or longevity, by protection from disease or by direct action upon fertility. Many attempts to show such direct action have been made using human blood group data but it appears that the majority of such effects are individually small. One observation is relevant to what follows about cattle fertility differences. Levine (1943) published figures suggesting an elimination of ABO incompatible children; there were relatively fewer A children counted when the mother was O and the father A than when the mother was A and the father O. In cattle a further complication of the differential fertility pattern may well be provided within the β-globulin system. In examining the data on which he was studying the inheritance of β-globulin types Ashton (1959) noticed that in certain matings involving the β-globulin A and β-globulin D alleles, where equal numbers of offspring like or unlike the mother would be expected, there was a disturbance of these normal segregation ratios. A consistent excess of offspring like the mother was obtained from such matings in both Friesian and Ayrshire cattle.

In similar matings involving the β^E allele this effect occurred when the E gene was present in the sire's genotype only. Where the mother's genotype included β^E a consistent lack of β^E offspring was found. Thus the E gene was at a particularly severe disadvantage and it will be recalled that this gene is relatively rare and in some breeds appears to have been totally eliminated.

These observations could reflect a selective elimination of fœtuses unlike their dams in respect of β-globulin type—a preference by the dam for fœtuses of her own type. In addition where the maternal genotype includes β^E then antagonism between β^E dam and β^E embryo causes a lowered viability of β^E embryos.

This observation has many features of great interest and fits very closely the known facts of bovine reproductive wastage. Ashton estimated the extent of this "mother preference" effect as sufficient to reduce viability of cattle conceptions to as low as 83%. This is consistent with estimates of bovine fœtal mortality which usually indicate that 20–30 out of every 100 matings fail within three months, despite successful fertilization.

In addition, if the returns to service following insemination are allocated to three periodicity classes, "short", "normal" and "long", fixed around a "normal" cycle length of eighteen to twenty-four days, then the proportion returning at "long" intervals can be taken as a crude index of the fœtal death-rate. Robinson (1957) has discussed this type of estimate. It is an interesting fact that the incidence of such long returns and, by implication, the fœtal death-rate it reflects appears to be a constant *irrespective of order number of insemination* (Ogden, 1959). If the ætiology of fœtal death was largely associated with infected, hormone deficient, nutritional deficient or other pathological conditions in the cow, then such affected individuals would increase in proportion with each repeat service. The fœtal mortality index should therefore rise with successive order number of insemination and the conception rate should fall abruptly. The fact that the index stays constant and the conception rate falls only very slightly lends support to the belief that reproductive wastage may well be largely genetic in character and that its rate is fixed by the random character of mating between different genotypes. Such wastage would operate at the same level irrespective of order number of insemination. Ashton's observations may provide a major example of the type of interaction between genotypes which, taken together, produce the "normal level of reproductive wastage". Efforts to break this normal pattern by controlling mating between and within the β-globulin phenotypes are at present in progress.

In this paper I have not attempted to be fully comprehensive but merely to indicate some of the main ways this type of data is being utilized. Recently there has been a fairly general realization of the lack of data on the incidence of the non-notifiable diseases of farm livestock which has led to the instigation of incidence surveys in cattle, sheep and pigs. It is possible that the time is approaching when some of the more simple of these marker techniques might be incorporated into these surveys so that the necessary incidence data which is proving costly

to collect will be available without expensive duplication.

For example, the possibility that one of the physiological functions of the β-globulins may be the transport of metals prompts the query as to whether incidence of the metabolic and deficiency diseases, so common in cattle, varies between the six β-globulin phenotypes. As with most subjects speculation is easy but proof difficult; the subject however is refreshingly diverse in content and the results already achieved in human medicine are proof of the rewards awaiting the veterinary investigator.

REFERENCES

ALLISON, A. C. (1954) *Brit. med. J.*, i, 290.
——, and AP REES, W. (1957) *Nature, Lond.*, **180,** 649.
ASCHAFFENBURG, R., and DREWRY, J. (1955) *Nature, Lond.*, **176,** 218.
——, —— (1957) *Nature, Lond.*, **180,** 376.
ASHTON, G. C. (1957) *Nature, Lond.*, **180,** 917.
—— (1958*a*) *Nature, Lond.*, **181,** 849; **182,** 370, 945, 1029, 1101.
—— (1958*b*) *Nature, Lond.*, **182,** 65.
—— (1958*c*) *Nature, Lond.*, **182,** 193.
—— (1959) *Nature, Lond.*, **183,** 404.
AUGUSTINSSON, K. B., and OLSON, B. (1958) *Biochem. J.*, **71,** 477, 484.
BANGHAM, A. D. (1957) *Nature, Lond.*, **179,** 467.
—— (1958) *Nature, Lond.*, **181,** 1551.
BLUMBERG, B. S., and TOMBS, M. P. (1958) *Nature, Lond.*, **181,** 683.
CABANNES, R., and SERAIN, C. (1955) *C.R. Soc. Biol., Paris*, **149,** 7.
EVANS, J. V. (1954) *Nature, Lond.*, **174,** 931.
——, HARRIS, H., and WARREN, F. L. (1957) *Biochem. J.*, **65,** 42P.
——, and KING, J. W. B. (1955) *Nature, Lond.*, **176,** 171.
——, ——, COHEN, B. L., HARRIS, H., and WARREN, F. L. (1956) *Nature, Lond.*, **178,** 849.
FISHER, R. A., and TAYLOR, G. L. (1940) *Nature, Lond.*, **145,** 590.
HARRIS, H., and WARREN, F. L. (1955) *Biochem. J.*, **60,** xxix.
JONXIS, J. H. P., *et al.* (1958) Meeting of the Netherlands Association for Hæmatology at Amsterdam, April 26. Reported in *Brit. med. J.*, i, 1113.
KING, J. W. B., EVANS, J. V., HARRIS, H., and WARREN, F. L. (1958) *J. agric. Sci.*, **51,** 342.
LANDSTEINER, K. (1936) The Specificity of Serological Reactions. London.
LEVINE, P. (1943) *J. Hered.*, **34,** 71.
OGDEN, A. L. (1959) Unpublished data.
PUTILIN, K. I. (1929) *J. Biol. Méd. exp., Moscou*, **5,** 1. Quoted by Allison and ap Rees (1957).
ROBINSON, T. J. (1957) Progress in the Physiology of Farm Animals. London; **3,** 847.
SAWIN, P. B., and GLICK, D. (1943) *Proc. nat. Acad. Sci., Wash.*, **29,** 55.
SMITHIES, O. (1955) *Biochem. J.*, **61,** 629.
VERZAR, F., and WESZECZKY, O. (1921) Cited by Wiener, A. S. (1943) Blood Groups and Transfusion. 3rd Edit. Springfield, Ill.

Dr. H. Lehmann (London):

Classification and Identification of Human Hæmoglobins

It has been known for 100 years that there were in existence two human hæmoglobins, one adult (A), the other fœtal (F). Following the discovery by Linus Pauling and his collaborators (1949) that sickle cells contained an abnormal hæmoglobin (S) which they could separate from normal adult hæmoglobin (A) by electrophoresis, a great number of other human hæmoglobins have been discovered by this method. Hörlein and Weber (1948) described a family with a hereditary methæmoglobinæmia where the methæmoglobin could not be reduced by chemical means. They found that by separating the hæm from the globin, and combining each with normal globin and hæm respectively, the abnormality was associated with the globin. This pigment is now called hæmoglobin M.

The last ten years have witnessed a rapid increase in the number of human hæmoglobins known, and there now seems no doubt that this number will increase more and more. We may well be nearest here to the individualization of human protein.

It is hoped that eventually some international agreement, or even an international organisation, will be established which will supervise the classification of these numerous human characters. Meanwhile an urgent need is to avoid a disintegration of nomenclature, and I intend to discuss the classification and identification of the human hæmoglobins.

The most important method in the differentiation of hæmoglobin variants is that of electrophoresis. At the very beginning of the discoveries of abnormal hæmoglobins it was found that this technique was fallible. When hæmoglobin D was discovered, it was stated that its electrophoretic properties were, in all respects, the same as those of hæmoglobin S, and the two have been differentiated by measuring the solubility of the ferro hæmoglobin, or by the sickling test (Itano, 1951). The brilliant work of Ingram (Ingram, 1956, 1957, 1958, 1959; Hunt and Ingram, 1958*a*, *b*) and Schroeder (Rhinesmith *et al.*, 1957; Rhinesmith *et al.*, 1958), has recently taught us a great deal about the nature of the globin molecule. The two mirror-image—but otherwise identical—half-molecules of globin (Kendrew and Perutz, 1957), each carry two peptide chains: (1) α—beginning with valine and leucine. (2) β—beginning with valine and histidine.

If, in one of these two chains, a single amino acid is changed from one carrying a negative

charge to one carrying no charge—or a positive charge—or *vice versa*—the electrophoretic properties of the hæmoglobin are fundamentally altered. The sixth amino acid of the β chain of normal adult hæmoglobin is the negatively charged glutamic acid. In hæmoglobin S the corresponding amino acid is the neutral valine, and in hæmoglobin C the positively charged lysine. Thus, with decreasing negative charge, the hæmoglobin moves less rapidly towards the positive pole on alkaline electrophoresis. Hæmoglobin D has not yet been fully analysed, but it is tempting to suggest that its electrophoretic properties—which are the same as in hæmoglobin S—are caused by the loss of a single negative charge.

This change can occur in a number of ways, and peptide analysis has shown that there are at least three different hæmoglobins D—all identical in their electrophoretic properties (Benzer *et al.*, 1958). Ingram (1959) has shown that these changes take place for D α in the α chain, and for D β in the β chain. It is clear from these considerations that we are approaching the time when it will be possible to define a hæmoglobin variant on the basis of its molecular structure. Meanwhile, however, more general procedures will have to be applied. The position resembles, in that respect, the one which we are encountering with the blood groups. Blood groups are determined by the very general procedure of agglutination, and only for blood groups A and B, the H substance, and the Lewis substance coating the red cell, do we have a more accurate amount of chemical information—thanks to another brilliant line of enquiries by Morgan, Watkins and others (Morgan and Watkins, 1959).

In 1953, a number of workers interested in hæmoglobins met and proposed that hæmoglobins should be designated by letters of the alphabet in order of their discovery, and these proposals met with universal acceptance (Chernoff *et al.*, 1953). However, difficulties arose when different hæmoglobins were given the same letter by their discoverers, or when two different designations were suggested for the same hæmoglobin.

In 1956, Neel, Zuelzer, and their collaborators (Robinson *et al.*, 1956), suggested one way out of this dilemma by naming two hæmoglobins "Liberian I" and "Liberian II" after their place of origin, subject to their final identification. Later, this led to their being called hæmoglobins N and K, (Ager and Lehmann, 1958). Yet another difficulty was that some of the electrophoretic differences are very small and, in fact, it has been suggested that a number of electrophoretically abnormal variants might be artifacts (Beaven and Gratzer, 1959). It is, however, difficult to accept that artifacts can occur in families, and should be under genetic control. As a temporary solution, until an accurate chemical classification can be produced, the following general nomenclature has been proposed by Ager, Lehmann and Vella (1958). They have divided the hæmoglobins into two major groups: fœtal and adult variants. The former show an ultra-violet spectrum of the fœtal type and include hæmoglobin F, the pigment of Fessas and Papaspyrou (1957), "Bart's" (Ager and Lehmann, 1958), and "Alexandra" (Fessas *et al.*, 1959; Vella *et al.*, 1959). The adult variants are divided into six groups according to their electrophoretic behaviour on paper electrophoresis at alkaline pH. These groups can be established by using as markers normal hæmoglobin and hæmoglobins H and S. Cells containing the abnormal hæmoglobins H and S can be identified independently from electrophoresis of their hæmoglobins. Hæmoglobin-H-containing cells can be recognized by their forming inclusion bodies under given conditions (Fig. 1A), and hæmoglobin-S-containing cells give a positive sickling test (Fig. 1B). The groups could be named I, II, III, &c., or they could have the name of the first hæmoglobin discovered within the group:

Group I	hæmoglobins moving more slowly than S	C group
Group II	hæmoglobins moving like S	S group
Group III	hæmoglobins moving between S and A ..	G group
Group IV	hæmoglobins moving like A	A group
Group V	hæmoglobins moving between A and H ..	J group
Group VI	hæmoglobins moving like H	H group

Within these groups hæmoglobins could again be numbered according to their mobility or, when they have the same mobility, they could be given (according to the time of their discovery) the additional letters, a, b, c, &c. The scheme tentatively proposed at the time was as follows:

Fœtal

F, "Fessas and Papaspyrou", "Bart's"

Adult

Group I or C group	"C group"
C, A'_2, E–A_2, O	1, 2, 3a, 3b, 4
Group II or S group	"S group"
S–D and its variants	a, b, &c.
Group III or G group	"G group"
L–P, G, Q	1a, 1b, 2, 3
Group IV or A group	"A group"
A–M	a, b
Group V or J group	"J group"
K, J, "Norfolk", N	1, 2, 3, 4
Group VI or H group	"H group"
H–I	a, b

Since then numerous new hæmoglobins have been discovered, perhaps the most important ones are the various abnormal methæmoglobins

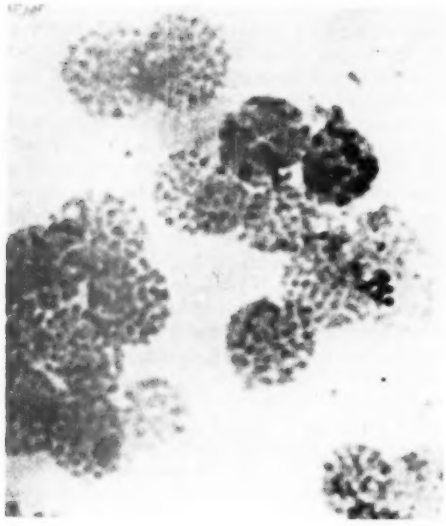

FIG. 1A.

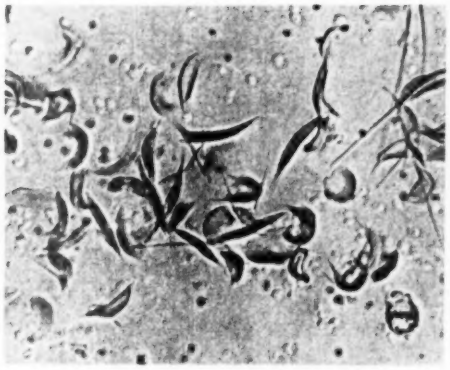

FIG. 1B.

FIG. 1.—Morphological features in red cells indicating presence of an abnormal hæmoglobin. A, Inclusion bodies, hæmoglobin H. B, Sickle cells, hæmoglobin S.

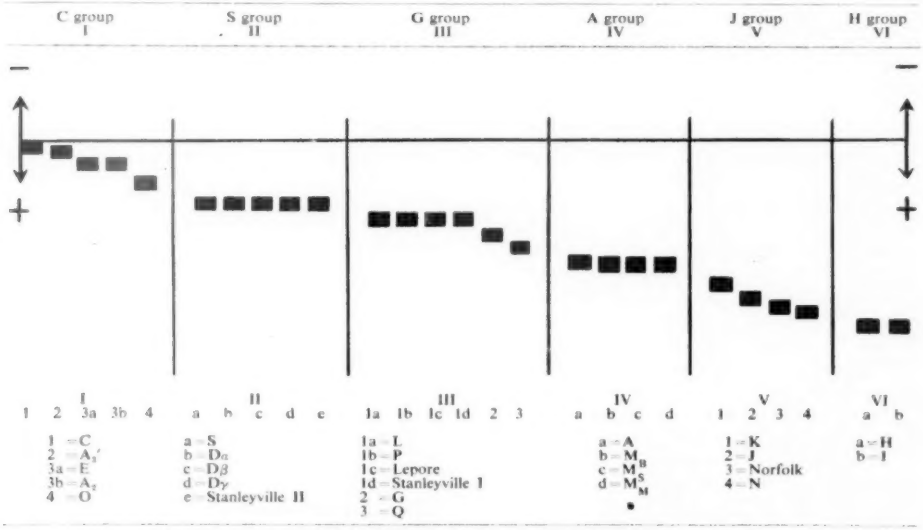

FIG. 2.—Pattern of adult hæmoglobins on paper electrophoresis pH 8·6.

(Gerald, 1958) (Fig. 2). When such a scheme is decided upon and, subsequently, a new hæmoglobin is discovered, this new pigment could then be allotted to one of the six groups, but a digit should only be assigned after full comparison and international agreement. It is obvious that it would remain the general practice to refer to the common and well-known hæmoglobins by their present names—S, C, D, E, &c.—but the more obscure pigments might well be labelled by giving the group a digit, and, if necessary, with the digit a small letter. If the new hæmoglobin was found between two to which a full designation had already been given, it could be indicated by an oblique sign. Thus, if after such a scheme was adopted a hæmoglobin was found

which moved, say, between hæmoglobins E, A_2, and O ("C Group" 3 and "C Group" 4), it would then have to be classified as "C group" 3/4. If it were possible to place a hæmoglobin between the hypothetical pigment "C group" 3/4 and O ("C group" 4), it could be designated "C group" 3/4/4.

Hæmoglobins which move identically at alkaline pH are at present differentiated by other methods. Examples are:

(1) Electrophoresis at acid pH: H and I.

(2) Chromatography at pH 6: L, P, Lepore, Stanleyville I.

(3) Examination of the spectrum: M_{Boston} $M_{Saskatoon}$ (or M_B and M_S).

(4) Peptide analysis: D_α, D_β, D_γ.

With the increasing number of methods brought to bear on the analysis of human hæmoglobin, we have to expect the discovery of more and more pigments, and we have here, in fact, a prime example of the individuality of human protein. In addition, numerous hæmoglobin variants have now been discovered within animal species, and it is likely that there will be even further expansion of the variety of hæmoglobins when this work is extended.

Thalassæmia

A much more difficult problem is that of classifying the thalassæmias. It is now generally accepted that classical thalassæmia must be due to a variety of genes which are usually found together, but which can occur in dissociation. One could quote numerous references, but particularly informative contributions are those by Gerald and Diamond (1958) and Ceppellini (1959). Of special interest are contributions to a symposium on abnormal hæmoglobins by Itano, Neel, and Zuelzer, respectively (1959). A very clear exposition of the problem has been given by Chernoff (1958) who describes the varieties of hypothetical genetic factors and their theoretical combinations as follows:

Hypothetical Genetic Factors in Thalassæmia	Theoretical Combinations	
A—Enzymatic defect: Fe-E. P. reaction	ABC/ABC ABC/abc	Cooley's anæmia Thalassæmia trait
B—Abnormalities of red cell morphology.	ABc/abc	Minimal thalassæmia, no Hb F
C—Fœtal hæmoglobin factor, &c.	aBC/abC	High Hb F, minimal symptoms, &c.

Another discussion has been that by Lehmann (1959) who reviewed particularly the dissociation between suppression of hæmoglobin A formation and changes in morphology in this condition. There is one condition found in Africa where morphological changes are absent, and suppression of hæmoglobin A in favour of other hæmoglobins is most pronounced: non-microcythæmic thalassæmia (Edington and Lehmann, 1955). The effect of a thalassæmia gene on hæmoglobin A production has been recognized for some years (Rich, 1952), but it has only recently been accepted that this has a very specific effect on hæmoglobin-A-containing cells (Lehmann *et al.*, 1959). The fact that thalassæmia seems to act on hæmoglobin A but not on hæmoglobins S or C suggests that its expression is associated with the presence of the normal hæmoglobin A β chain. One would therefore expect that in an abnormal hæmoglobin in which the α chain is altered and in which the β chain is normal, thalassæmia would have an effect. Hæmoglobin J has not yet been investigated as to whether its specific difference from hæmoglobin A is found in the α or in the β chain. Sanghvi *et al.* (1958) have described a woman who was heterozygous for hæmoglobins A and J, and who was also heterozygous for the thalassæmia gene, yet there was no hæmoglobin J thalassæmia. If the specific alteration in hæmoglobin J was in the α chain, then it would carry a normal β chain, and the thalassæmia gene would act equally on A and J, and one would find no change in the proportion of the two hæmoglobins.

It is not yet possible to attempt anything like a classification of thalassæmia. Indeed, there may be one thalassæmia type acting on the α chain rather than on the β chain. Even the inheritance of thalassæmia is not yet clear, and doubt has been cast on whether the mode of inheritance is uniform. It seems that in some instances thalassæmia is inherited independently from hæmoglobins S and C, and in some instances that there is a linkage between the two (Neel, 1958).

References

Ager, J. A. M., and Lehmann, H. (1958) *Brit. med. J.*, i, 929.

——, ——, and Vella, F. (1958) *Brit. med. J.*, ii, 539.

Beaven, G. H., and Gratzer, W. B. (1959) *J. clin. Path.*, **12**, 1.

Benzer, S., Ingram, V. M., and Lehmann, H. (1958) *Nature, Lond.*, **182**, 852.

Ceppellini, R. (1959) Symposium Geneticæ Hæmatologicæ. Acta Geneticæ Medicæ et Gemellologiæ. Rome; suppl. II, p. 47.

Chernoff, A. I. (1958) Conference on Hemoglobin. National Academy of Sciences—National Research Council. Washington, D.C.; p. 283.

——, *et al.* (1953) *Blood*, **8**, 386.

Edington, G. M., and Lehmann, H. (1955) *Brit. med. J.*, i, 1308; ii, 1328.

FESSAS, Ph., MASTROKALOS, N., and FOSTIROPOULOS, G. (1959) *Nature, Lond.*, **183,** 30.
——, and PAPASPYROU, A. (1957) *Science*, **126,** 1119.
GERALD, P. S. (1958) *Blood*, **13,** 936.
——, and DIAMOND, L. K. (1958) *Blood*, **13,** 835.
HÖRLEIN, H., and WEBER, G. (1948) *Dtsch. med. Wschr.*, **73,** 476.
HUNT, J. A., and INGRAM, V. M. (1958*a*) *Biochim. biophys. Acta*, **28,** 546.
——, —— (1958*b*) *Nature, Lond.*, **181,** 1062.
INGRAM, V. M. (1956) *Nature, Lond.*, **178,** 792.
—— (1957) *Nature, Lond.*, **180,** 326.
—— (1958) *Biochim. biophys. Acta*, **28,** 539.
—— (1959) *Brit. med. Bull.*, **15,** 27.
ITANO, H. A. (1951) *Proc. nat. Acad. Sci., Wash.*, **37,** 775.
—— (1959) In: Jonxis and Delafresnaye (1959) p. 12.
JONXIS, J. H. P., and DELAFRESNAYE, J. F., eds. (1959) Abnormal Hæmoglobins. Oxford.
KENDREW, J. C., and PERUTZ, M. G. (1957) *Annu. Rev. Biochem.*, **26,** 327.
LEHMANN, H. (1959) *Brit. med. Bull.*, **15,** 40.
——, *et al.* (1959) In: Jonxis and Delafresnaye (1959), discussion pp. 318–19.
MORGAN, W. T. J., and WATKINS, W. M. (1959) *Brit. med. Bull.*, **15,** 109.
NEEL, J. V. (1958) Conference on Hemoglobin. National Academy of Sciences—National Research Council. Washington, D.C.; p. 253.
—— (1959) In: Jonxis and Delafresnaye (1959) p. 158.
PAULING, L., ITANO, H. A., SINGER, S. J., and WELLS, I. C. (1949) *Science*, **110,** 543.
RHINESMITH, H. S., SCHROEDER, W. A., and MARTIN, N. (1958) *J. Amer. chem. Soc.*, **80,** 3358.
——, ——, and PAULING, L. (1957) *J. Amer. chem. Soc.*, **19,** 4682.
RICH, A. (1952) *Proc. nat. Acad. Sci., Wash.*, **38,** 187.
ROBINSON, A. R., ZUELZER, W. W., NEEL, J. V., LIVINGSTONE, F. B., and MILLER, M. J. (1956) *Blood*, **2,** 902.
SANGHVI, L. D., SUKUMARAN, P. K., and LEHMANN, H. (1958) *Brit. med. J.*, ii, 828.
VELLA, F., AGER, J. A. M., and LEHMANN, H. (1959) *Nature, Lond.*, **183,** 30.
ZUELZER, W. W. (1959) In: Jonxis and Delafresnaye (1959) p. 100.

Professor C. Rimington (London):

Congenital Porphyria in Animals

Congenital porphyria is a rare disease in man, the world literature only recording some 36 cases altogether. Its occurrence in animals was presumed from reports of porphyrin-stained bones seen after slaughter at abattoirs but no living case in any species had been recorded up to 1935. In this year Fourie and I encountered a herd of grade Shorthorn cattle in Swaziland in which 13 living animals had the disease (77% males), all being the progeny of the same bull who appeared clinically normal. The animals, which were described clinically by Fourie (1936), were bought by the Onderstepoort Veterinary Research Laboratory and one was slaughtered for detailed chemical investigation (Rimington, 1936). All features of the disease resembled very closely those of the human congenital porphyria patient described by Fischer *et al.* (1925) and Borst and Königsdörfer (1929). There was excessive production of uroporphyrins and coproporphyrins, mainly of the isomeric series I. The teeth and bones were reddish-brown due to deposition of uroporphyrin, fluorocytes were present in the bone marrow and there were lesions due to photosensitization.

Enquiry showed that cases had appeared in the first generation derived from the Shorthorn bull (No. 7015) but that the farmer had previously used a bull bred from the same stock as 7015. The evidence concerning inheritance was thus not clear, so controlled breeding experiments were undertaken. The first affected calf so to be produced was a female, the progeny of bull 7015 and one of his clinically normal daughters. This was her first pregnancy and subsequent matings with 7015 produced two normal calves. The affected calf had pink teeth at birth and normal-coloured urine but one month later the urine was pink in colour.

The second affected calf, a male, resulted from crossing a daughter of bull 7015 with one of his sons out of a normal unrelated female. This was her third calf, the two preceding ones (by bull 7015) having been normal. A third calf was obtained by an eventually successful mating of bull 7015 with one of his own daughters which was herself a porphyric. It died after ten days and the whole skeleton was deeply pigmented. The evidence thus indicated inheritance of the disease as a Mendelian recessive character and was supported by the fact that crossing bull 7015 with ten normal and unrelated females resulted in eight normal calves.

Very soon after the discovery of the Swaziland herd of red Shorthorns, another quite unrelated case was encountered in South Africa in a black and white grade Friesland cow, Cedara Ria 4th (Fourie and Rimington, 1938). The lesions of photosensitization were confined to the white areas of skin. In the following year Flight (1939) observed two more cases among Frieslands in the Ladysmith area. These were heifers sired by a bull named Kamnatie Charles out of his own normal daughters. He was therefore very probably a carrier of the recessive gene and it seemed also likely that some blood relationship might exist between him and the Cedara case. Records were accordingly searched and common ancestry was indeed found in the bull Albert 1306 H. This bull was five generations removed from the affected Cedara Ria 4th and four generations from Kamnatie Charles. This brief review of the genetics of the South African cases summarizes evidence for the transmission of

congenital porphyria as a Mendelian recessive character in two bovine breeds (*see* Fourie, 1939).

Congenital porphyria may also occur in pigs. It has been reported by Clare and Stephens (1944) in New Zealand and by Jörgensen and With (1955) in Denmark. Since, however, studies in this species have been less comprehensive, I shall do no more than quote Jörgensen and With's interesting statement, "the heredity of the condition is not quite clear; but our observations point towards a single dominant gene, although a more complicated mechanism cannot be excluded". Jörgensen and With (1955) also found bovine congenital porphyria in the same part of Denmark and state that it is inherited as a Mendelian recessive character as is the South African disease.

England had no record of living cases until 1957 when Ross (1957) described post-mortem examination of a slaughtered roan Shorthorn heifer, presumed from the result to have been a case of congenital porphyria. Both parents were already dead. Three living cases in a herd of pedigree Shorthorn dairy cattle were discovered on a Buckinghamshire farm in the same year and have been described by Amoroso *et al.* (1957). The inheritance has been relatively easy to trace and follows the course of a Mendelian recessive as in South Africa; two successive bulls, X and Y, had been obtained from the same breeder and these had a common ancestor on the maternal side in bull Z. All cases resulted from crosses between bull Y and daughters of X. From one such pregnancy, twins were born, one normal and one affected, thereby providing the ideal control for the biochemical studies we have carried out. Hæmolysates prepared from these animals' red cells have been incubated with porphobilinogen or δ-aminolævulic acid when series III porphyrins only are produced from the normal blood but a mixture of series I and series III porphyrins from the congenital porphyria blood. The enzymic defect thus persists in the matured cells after they have left the bone-marrow. Further cases of congenital porphyria may confidently be expected to turn up among Shorthorns in other parts of England. Indeed Heath (1959) has recently discovered some in Westmorland.

A final reference must be made to bovine congenital porphyria in America and in Jamaica. Two cases in Holsteins were noted in California (Rhode and Cornelius, 1958; Schalm, 1956) and a group in Michigan have observed an additional eleven cases (cited by Nestal, 1958). In Jamaica, Nestal (1958) has reported three cases in Jamaica red cattle and two in Jamaica blacks but in neither instance were there breeding records adequate to establish the type of inheritance. Watson *et al.* (1958) have compared some of the American cases with human congenital porphyria and find general similarity. In the one affected cow thus far splenectomized, however, no significant reduction of porphyrin excretion was observed.

As suggested many years ago (Rimington, 1936, 1938) the biochemical defect in congenital porphyria is a deficiency of an enzyme in the hæmopoietic system. This directs transformation of porphobilinogen into the asymmetrical III series isomer of uroporphyrin; in its absence uroporphyrin I is formed. The uroporphyrin decarboxylase, converting uroporphyrins into coproporphyrins is not isomer-specific so that both uroporphyrin I and coproporphyrin I accumulate in the animal with congenital porphyria. Production of protoporphyrin only occurs enzymatically, however, from coproporphyrin III hence the blood of affected animals contains only normal hæm derived from III series protoporphyrin. A complete inability to synthesize III series porphyrin would be incompatible with life; evidence presented by Schmid *et al.* (1955) suggests that in congenital porphyria some erythroblasts are normal, others abnormal and that splenectomy does not alter this ratio but merely slows down the destruction of the abnormal, porphyrin-rich cells so lowering total porphyrin excretion without influencing the primary metabolic disturbance.

REFERENCES

Amoroso, E. C., Loosmore, R. M., Rimington, C., and Tooth, B. E. (1957) *Nature, Lond.*, **180,** 230.

Borst, M., and Königsdörfer, H. (1929) Untersuchungen über Porphyrie. Leipzig.

Clare, T., and Stephens, E. H. (1944) *Nature, Lond.*, **153,** 252.

Fischer, H., Hilmer, H., Lindner, F., and Pützer, B. (1925) *Hoppe-Seyl. Z.*, **150,** 44.

Flight (1939) *J. S. Afr. vet. med. Ass.*, **10,** 106.

Fourie, P. J. J. (1936) *Onderstepoort J. vet. Sci.*, **7,** 535.

—— (1939) *Onderstepoort J. vet. Sci.*, **13,** 283.

——, and Rimington, C. (1938) *Onderstepoort J. vet. Sci.*, **10,** 431.

Heath, G. B. S. (1959) Personal communication.

Jörgensen, S. K., and With, T. K. (1955) *Nature, Lond.*, **176,** 156.

Nestal, B. L. (1958) *Cornell Vet.*, **48,** 430.

Rhode, E. A., and Cornelius, C. E. (1958) *J. Amer. vet. med. Ass.*, **132,** 112.

Rimington, C. (1936) *Onderstepoort J. vet. Sci.*, **7,** 567.

—— (1938) *C.R. Lab. Carlsberg* (sér. chim.), **22,** 454.

Ross, D. B. (1957) *Vet. Rec.*, **69,** 345.

Schalm, O. W. (1956) In: Diseases of Cattle. Edited by M. G. Fincher *et al.* Evanston, Ill.; p. 355.

Schmid, R., Schwartz, S., and Sundberg, D. (1955) *Blood*, **10,** 416.

Watson, C. J., Perman, V., Spurrell, F. A., Hoyt, H. H., and Schwartz, S. (1958) *Trans. Ass. Amer. Physns*, **71,** 196.


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Meeting
June 4, 1959

Prevention and Treatment of Motion Sickness

By E. M. GLASER, M.C., Ph.D., M.D., M.R.C.P.
London

MOTION sickness is unique among all illnesses that afflict man. In common with childbirth (which is not normally considered an illness), it can cause complete temporary incapacitation without any pathological basis and entirely by reflex mechanisms, though unlike childbirth it serves no obvious purpose at all. In common with childbirth, also, motion sickness excels in the variety of useless procedures advocated for its prevention. Not only has every substance with a known pharmacological action been tried at some time or other for the prevention and treatment of motion sickness, but almost everything that can be swallowed (*Brit. med. J.*, 1952), as well as quite a few substances which ought not to be swallowed. Creosote (Maddock, 1837), a mixture of vinegar and salt (*Lancet*, 1843) and a mixture of hydrocyanic acid, nitric acid, hydrochloric acid, and magnesium sulphate (Hocken, 1861) take pride of place among nineteenth century treatments, but even quite recently a pill has been advertised in this country which contained among other things minute quantities of petroleum and nicotine, while a writer in a medical journal has seriously suggested that chewing gum might be beneficial (Monto, 1947). Not so long ago brandy, gin, or champagne, pilocarpine, ergotamine, belladonna and luminal were all advocated, together with several other substances, in one paper (Hill, 1936), and others advised bizarre procedures, such as salt water baths (Bennett, 1928), tight compression of the neck (Genee, 1924), packing of ears with cotton-wool (Lemon, 1919), or injections of sodium bicarbonate (Hasegawa, 1949). However, pride of place among all remedies must go to a mid-Victorian one containing horseradish and flavoured with red herrings (*Brit. med. J.*, 1862).

The Reflex of Motion Sickness

There have been recent reviews on this subject by Borison and Wang (1953) and Chinn and Smith (1955).

The receptors from which the reflex of motion sickness originates are undoubtedly in the vestibular apparatus of the ear. This was suspected by Purkinje in 1820 and much evidence has been collected about it since. Deaf-mute people or patients suffering from Ménière's syndrome do not develop motion sickness, nor do dogs after destruction of their vestibular apparatus. It has also been known for a long time that the reflex stimulus is linear acceleration, especially in the sagittal plane, and this was first suggested in 1875 by Wilks when lifts were a new invention. A few years later Irwin (1881) suggested the term "motion sickness", for he knew that the sickness was the same, whatever the cause of the acceleration. Irwin had probably seen motion sickness elsewhere than in lifts and at sea, even though motor cars and aeroplanes did not exist then; in our time royalty are said to have commented that state coaches swayed uncomfortably, and an old lady has recently told me that she was always sick as a child some sixty years ago when travelling to Scotland by express train.

We know now that the receptors for motion sickness are in the vestibular apparatus, chiefly in the utricle, where the otolith, like a little pebble, rests upon hairlike nerve receptors—an organ exquisitely suited to record linear accelerations. Of course, the vestibular apparatus normally serves ordinary postural reflexes, but there is a complex reflex pathway for motion sickness involving the cerebellum and the brain-stem, and there must be pathways to the cerebral hemispheres transmitting the sensation of nausea. The efferent fibres cause relaxation of the stomach, contractions of the duodenum, and sharp contractions of the abdominal muscles, accompanied by closing of the glottis and opening of the mouth, which leads to the emission of gastric and duodenal contents. This reflex vomiting is, of course, the essential process of motion sickness, but nausea usually precedes vomiting and it is an integral part of motion sickness. Once in a while explosive vomiting may come before nausea, but at some stage or other nausea is always present. In 300 men who were exposed to motion sickness some 1,600 times we have found that those who were seen

to vomit by trained observers always reported having felt nausea. About 20% of untreated people exposed to severe wave motion for periods of about one hour feel sick without actually vomiting or retching (Glaser and Hervey, 1951, 1952; Glaser and McCance, 1959). Relief from nausea should thus be part of the treatment of motion sickness. Other symptoms, especially dizziness, sleepiness and headache, are more frequent in people suffering from motion sickness than in people who are not sick, irrespective of treatment given, but these symptoms can be confused with side-effects of drugs (Glaser, 1953) and they can be caused by anxiety or by the arousal of interest in such symptoms (Glaser and Whittow, 1954), so that they cannot be considered an integral part of the specific reflex of motion sickness. Equally sweating and diarrhœa, which often precede or accompany vomiting, are not specific, but probably a result of generalized central nervous excitation.

As in all complex reflexes, impulses from different parts of the body may contribute to motion sickness. It is well known that movements of the eye muscles or of the muscles supporting the body can aggravate motion sickness, and it seems probable indeed that the very basis of motion sickness is a divergence of information from different sensory afferents (Walsh, 1957), though the distortion of visual images may play some part in causing symptoms (Miller and Goodson, 1958). Smells seem to make motion sickness worse, and so can anxiety. The effects of interest and anxiety upon reflex responses are not fully understood, but there is evidence that responses and habituation of responses can both be modified by activities of the brain (Glaser *et al.*, 1959). Everybody who has had experience of motion sickness knows how it can stop while a person suffering from it is occupied and how it gets worse when there is nothing to do except worry.

Many reflexes are modified by repeated usage of the reflex pathways. There is indeed experimental evidence that reflex pathways are facilitated by usage (Eccles, 1953) and it is possible that people may acquire the habit of being sick, so that whenever they travel on a given type of transport they suffer from nausea or vomiting. It is known also that reflexes can be conditioned, which means that they are elicited by stimuli other than the normal reflex stimulus. Thus a person who has often been very sick from the motion of a ship may become sick again at the sight or smell of a ship.

Habituation

Fortunately facilitation of motion sickness by previous experience is rare, and there is a more important mechanism, habituation, which consists of a diminution of responses to repeated or continued stimuli, probably through facilitation of inhibitory pathways which have been extensively used. This helps to bring about some improvement in most people after repeated or prolonged exposures to wave motion (Hill, 1936; Hill and Guest, 1945; Glaser and Hervey, 1952; Glaser and McCance, 1959). Evidence obtained in controlled experiments suggests the possibility that habituation to motion may take place even if sickness is inhibited by drugs.

Habituation must play an important part in reducing motion sickness among those who travel much on various forms of sick-making transport, and it seems possible also that habituation is the reason why young people are generally more prone to motion sickness than older ones and children more than grown-ups. The older we are, the more likely we are to have experienced a thing before; the more often we have experienced a stimulus, the less likely are we to produce an excessive response. There are of course other processes of ageing, but one phenomenon of maturity is a gradual lessening of the violence of one's responses, and habituation must play some part in this (Glaser, 1958). Experimental habituation to various stimuli probably wears off after several days or a few weeks, and the ability to habituate varies in different people, but if a person has frequently become habituated to a stimulus he is likely to retain at least an increased facility to habituate to it again. The process resembles learning (Glaser and Whittow, 1957; Glaser, 1958). Anything once learnt and soon forgotten is learnt more easily next time, and anything that has been often learnt is unlikely to be forgotten again. Thus, each habituation may help to achieve the next, and eventually habituation could persist for long periods.

Unfortunately, however, habituation is highly specific, so that it takes place only with regard to a precise stimulus (Glaser *et al.*, 1959). It follows from this that habituation to one kind of motion will not necessarily protect against another kind of motion, and indeed habituation to swings was shown to give no protection at sea (Gibson *et al.*, 1944). Herein lies perhaps the explanation why people who are used to the short-period accelerations of small ships are sometimes sick on large ones which oscillate at longer periods and accelerate and decelerate at different rates. Similarly those who are good sailors on large ships, often find themselves sick on small boats or in aeroplanes.

Prevention and Treatment Based on Physiological Mechanisms

An understanding of the physiological

mechanisms which have just been discussed suggests several ways of inhibiting motion sickness. Obviously those who favour lying in one's bunk and those who favour standing up on deck are both right, since lying down will reduce vestibular stimulation, while standing up and looking at the sky or the horizon will accelerate habituation and reduce visual distortion. Equally, of course, both these views are wrong, because lying down will prevent habituation while standing up will facilitate nausea and vomiting. The best method on sea journeys is to do both and to take a pill as well. The procedure which seems the most logical to me is to take a pill when the sea is rough and lie down until it is taking effect, but to go on deck as soon as possible in order to become habituated.

From what is known about the influence of the brain on reflexes, it follows also that interesting activities can help to prevent motion sickness by drawing the patient's attention away from his symptoms. Conversely, anxiety, or various other stimuli which would not normally cause vomiting, may trigger off the reflex when the motion alone would not have been enough for this: the smell of burnt fat on a ship, or the sight of a swaying curtain on an aeroplane, or the offer of a squashed cream bun on an alpine bus, can produce sudden explosive vomiting in people who until then have successfully fought their sickness.

Habituation cannot help those who are highly susceptible but who travel rarely and for short periods only. Fortunately under such conditions prevention of motion sickness by drugs is effective (*see below*), but there could be another approach to this problem. Since people are less liable to be sick when they are lying down and happy and interested than if they are standing up and anxious or bored, it might be possible to prevent motion sickness on steamers crossing the Irish Sea or English Channel, or carrying troops on invasion exercises across narrow rough waters, by making people lie down while their attention was held by cinema or television screens placed horizontally along the ceiling or along both sides of the hold. If it worked, this could counteract the disadvantages of using drugs on short journeys, namely side-effects persisting after the motion has ceased.

Drugs

Therapeutic tests are always difficult but never more so than in the study of motion sickness. For short exposures adequate techniques exist, beginning with the classical controlled trials of Holling *et al.* which were carried out early in the last World War and published in 1944. More recent tests include complete crossing over, so that each drug is given in turn and in random order to every subject, and careful control of every detail, down to the subjects' food and previous activities (Glaser and Hervey, 1951, 1952; Glaser and McCance, 1959). For long journeys the design of experiments is more difficult still, and it is probably true to say that there have been no wholly satisfactory experiments under those conditions.

A crucial problem in all tests of remedies for motion sickness is the time which must elapse between administration of drugs and exposure to motion. In our experiments involving short exposures to wave motion, care was taken that all drugs should be at their peak action (Glaser and Hervey, 1951; Glaser and McCance, 1959), but in experiments on long journeys it was sometimes doubtful whether drugs which take a long time to act were given early enough to be effective at the beginning of the journey, or whether drugs which have a short action protected the subjects during the whole of the journey. In certain cases there is clear evidence that certain drugs could not have been effective for such reasons. Thus in experiments on troopships (Report, 1956) in which 16,920 tests were conducted by 21 authors testing 26 treatments, no drug which is eliminated or detoxicated within twelve hours could have had any effect at all, because drugs were given on sailing and at mealtimes, so that only those subjects who had taken a long-acting drug on the previous night were protected before and during the morning meal, when people are the most likely to be sick.

Another possible source of error is the variability of wave motion. Except in experimental tanks or on swings the wave motion can never be quite constant, but careful design can ensure that within one experiment the effects of variable wave motion should be equally distributed (Strickland *et al.*, 1950; Glaser and Hervey, 1951; Chinn *et al.*, 1952, 1953; Report, 1956). However, when the motion is mild, the difference between the most effective and less effective drugs can be hidden, since a comparatively ineffective drug, or a comparatively small dose of an effective one, may be enough under such conditions. Thus, in order to interpret the results of experiments, it is necessary to know how severe the wave motion was. In recent years experiments on motion sickness have frequently included data about the accelerations and the oscillations met (Glaser and Hervey, 1951, 1952; Chinn *et al.*, 1952; Shaw, 1954; Glaser and McCance, 1959), but it is often difficult to interpret results without such data. When the number of subjects who are sick after having taken a dummy substance is small, the possibility must always be admitted that the wave motion was not severe enough to show up differences between less and more

effective drugs. This casts further doubts on experiments involving 15 Atlantic crossings (Report, 1956) in which some drugs were tested only when the incidence of vomiting among those receiving a dummy was comparatively low. Thus 15% of controls were sick when hyoscine was tested, 21% on all trips and 44% on one trip.

A further difficulty follows from what has just been said. On long journeys in large ships the wave motion is frequently mild, or during part of such journeys people may be habituated to motion. Under those conditions they may indeed be better off with a milder form of treatment than with powerful medication. There is reason to believe that all remedies for motion sickness owe their effect to a hyoscine-like central nervous action (Bain, 1952; Glaser, 1953), and that the effectiveness of a drug in the presence of wave motion is directly related to this hyoscine-like action. There is clear evidence also that the most powerful remedies have the fewest side-effects in the presence of sharp wave motion (Glaser and Hervey, 1951, 1952; Chinn *et al.*, 1953; Glaser and McCance, 1959) but that once the motion ceases the best remedies for motion sickness have the most side-effects (Glaser, 1953). It seems reasonable to conclude that strong remedies may have a similar effect when the motion is mild to that when there is no motion at all (Glaser, 1955); thus in the presence of mild wave motion or in people who are accustomed to the motion, powerful drugs might give rise to side-effects.

It is pertinent to ask, then, whether any clear recommendations can be made about the prevention and treatment of motion sickness. For short exposures 0·6–1 mg. of hyoscine hydrobromide is without any doubt the best remedy when the motion is sharp or the susceptibility of the patients high. By short exposure is meant a period covered by a single dose of the drug, or anything up to four to six hours. There are few therapeutic recommendations in the whole field of medicine which can be made with such confidence, as there is no drug now in general use which has not been significantly less effective under such conditions than 0·6–1 mg. of hyoscine (Holling *et al.*, 1944; Hill and Guest, 1945; Tyler, 1946; Strickland *et al.*, 1950; Chinn and Oberst, 1950; Glaser and Hervey, 1951, 1952; Chinn *et al.*, 1953; Glaser and McCance, 1959). Surprisingly, perhaps, since the evidence is so overwhelming, disagreement is constantly being expressed with this conclusion. Thus, when promethazine was found to be less effective than hyoscine, it was suggested that giving promethazine one and a half to two hours before exposure to motion was not enough to allow complete absorption of promethazine though the drug was taken three hours after a light meal (Bethell, 1951). When meclozine hydrochloride was found to be completely ineffective in doses of 25 mg. it was claimed that one and three-quarters to two hours was not enough for absorption of that drug four hours after a light meal (*Chemist and Druggist*, 1959), though even one hour is probably enough between the taking of meclozine and exposure to motion (New and Nonofficial Drugs, 1958). Hyoscine hydrobromide 1 mg. was found to give significant protection if taken only five to ten minutes before exposure to motion (Glaser and Hervey, 1952), and it is unlikely that other drugs should not be absorbed two hours after being taken on an empty stomach.

Claims have also been made that hyoscine hydrobromide in doses of 0·6–1 mg. gives rise to side-effects, but controlled experiments have invariably shown that in the presence of wave motion hyoscine causes fewer side-effects, apart from dryness of the mouth, than any other substance, fewer even than lactose dummies (Strickland *et al.*, 1950; Glaser and Hervey, 1951, 1952; Chinn *et al.*, 1953; Glaser and McCance, 1959).

My colleagues and I have given hyoscine hydrobromide in doses of 0·75–1 mg. both on land and in the presence of wave motion about 600 times, while the literature contains records of about 1,500 subjects who had been given 0·6–1·2 mg. of hyoscine hydrobromide without any ill-effect (*see* Glaser, 1955; Glaser and Newling, 1955; Glaser and McCance, 1959). Payne and Hauty (1953) and Payne and Moore (1955) found no more impairment of performance after 0·65 mg. of hyoscine hydrobromide than after a dummy or after motion sickness remedies of the antihistamine type, and even 1·2 mg. of hyoscine was found not to hamper skilled performance (Holling *et al.*, 1944).

Continued administration of hyoscine hydrobromide for four days in doses of 2 mg. on the first day and 1·5 mg. daily thereafter was found to have no ill-effects in healthy people on land in a controlled experiment in which all observed data were reported (Glaser, 1953); this was contradicted in experiments at sea, though without giving complete quantitative data (Handford *et al.*, 1954; Report, 1956). But few people need treatment at sea for many days because useful remedies allow habituation (*see above*), and ill-effects from continued administration of hyoscine are thus hypothetical in any case.

Various antihistamine substances have been useful, but not all are effective against motion sickness. Such effectiveness is not related to histamine antagonism but, as has been already suggested, to an incidental hyoscine-like action.

The first antihistamine substance to be given against motion sickness was probably mepyramine maleate (Anthisan) (McEvedy, 1949), but dimenhydrinate (Dramamine) was the first to be widely hailed as a new advance in the prevention and treatment of motion sickness (Gay and Carliner, 1949*a*, *b*). Dimenhydrinate is the 8-chlorotheophyllinate of diphenhydramine hydrochloride (Benadryl), and both these salts, in doses ranging from 25 mg. of the hydrochloride to 100 mg. of the 8-chlorotheophyllinate have been found to be significantly less effective than hyoscine hydrobromide 0·6–1·0 mg. at sea and in the air (Strickland *et al.*, 1950; Chinn and Oberst, 1950; Glaser and Hervey, 1951; Chinn *et al.*, 1953), while causing greater disturbance of co-ordination and performance (Payne and Moore, 1955).

An undoubtedly effective drug is promethazine hydrochloride (Phenergan) in single doses of 25 mg. (Glaser and Hervey, 1951; Chinn *et al.*, 1953). It has also been effective on long journeys in two or three daily doses of 25 mg. (Report, 1956), though under the conditions of those experiments this was partly due to its comparatively long action (*see above*). Smaller doses of promethazine may be used, but giving more than 25 mg. does not help (Glaser and Hervey, 1952). Promethazine - 8 - chlorotheophyllinate (Avomine) is also used, but the theophyllininate is insignificant in amount and is ineffective against motion sickness even in larger doses.

More recently cyclizine hydrochloride (Marzine) has been tested in doses of 50 mg., and it provides significant protection in people who are already slightly habituated to the motion, though it appears to be ineffective on first exposure to sharp wave motion (Glaser and McCance, 1959). Thus its value may be the greatest when powerful medication is not needed. It too has a moderately long duration of action and it was thus effective in experiments at sea which favoured long-acting drugs when the motion was frequently mild (Report, 1956).

Meclozine hydrochloride (Ancolan, Meclizine, Sealegs, Postafene) has also been widely tested. On long journeys it was found effective in doses of 25 or 50 mg. once or twice daily (Report, 1956; Arner *et al.*, 1958), and, as has been said above, this was partly due to its very long action. 50 mg. of meclozine was significantly less effective against airsickness than 1 mg. of hyoscine hydrobromide (Chinn *et al.*, 1953) but the two drugs were given under conditions which were not exactly the same. Those testing meclozine at sea did not report any undue side-effects from repeated 50 mg. doses (Report, 1956), but the makers of this substance consider 25 mg. to be the safe dose and in that dose, taken one and three-quarter hours before the motion began, meclozine hydrochloride was ineffective (Glaser and McCance, 1959), whether the subjects were habituated to the motion or not. Even if it was assumed that a better effect might have been obtained if the drug had been taken many hours before exposure to motion or if a larger dose had been taken (though there is nothing to justify the former assumption and little to justify the latter), it would seem unwise to use meclozine. There are other substances which are certainly effective in doses which are undoubtedly safe and which need not be taken so early that there might be some uncertainty whether rough motion will be met. Moreover, it would seem unwise to take a drug which under some circumstances might continue to have effects even on the next day after the motion had ceased. The fact that meclozine is sold without prescription in this country and that it is advertised to laymen is very disturbing.

All this means that those who fear hyoscine for long exposures would be best advised to use promethazine or cyclizine, though there is no clear and statistical evidence against hyoscine and some evidence that it is safe for up to four days. Those who require only mild medication might also find promethazine or cyclizine adequate. Combinations of hyoscine with antihistamine substances appear to offer little advantage (Glaser and Hervey, 1952) and they may interfere with efficiency (Payne and Moore, 1955).

Nothing has been said so far about the ability of drugs to treat sickness once vomiting has begun, and there is very little controlled experimental evidence about this. As mentioned above, hyoscine hydrobromide 1 mg. gives significant protection when compared with a dummy substance if given five to ten minutes before exposure to sharp wave motion (Glaser and Hervey, 1952). Absorption might not be equally rapid in a person who is seasick though not vomiting, but this suggests the possibility that hyoscine might be used to treat motion sickness, and there is evidence, indeed, that adequate amounts of this drug are retained if it is taken immediately after a bout of vomiting and if the patient lies down for about one hour (Glaser, 1952). A preparation containing hyoscine has also been successfully given on long sea journeys, both prophylactically and therapeutically for seventy-two hours (Gruhler, 1955). Hyoscine happens to be well tolerated by children and it has been successfully given in doses of 0·25 mg. to treat seasick children under three years (Glaser, 1952). In severe vomiting the drug would have to be

given by suppositories or by injection, and some remedies are available in such a form.

Summary

Motion sickness is a reflex which originates from impulses in the vestibular apparatus, chiefly in the utricle. It consists of vomiting and is accompanied by nausea. Severe nausea on its own justifies treatment even in the absence of vomiting. Like all reflexes, motion sickness may be modified by impulses from the cerebral hemispheres, the most important of which are the inhibition of motion sickness by interest in other things, the enhancement of motion sickness by interest in one's symptoms or by anxiety, and the diminution of motion sickness by habituation to wave motion. It follows that some lessening of motion sickness can be achieved by lying down (when vestibular stimulation is the least), by interesting activities, and by habituation to the motion. Since habituation is more rapid when the head is held up, it seems best to lie down until treatment by drugs has taken effect and then to get up in order to allow habituation.

For severe motion at sea or in the air and during exposures lasting not more than a few hours, single doses of hyoscine hydrobromide 0·6–1·2 mg. have invariably been found significantly more effective than any other drug available at present. Such single doses are also accompanied by fewer side-effects than any other drug and by little or no impairment of efficiency, but in the absence of wave motion hyoscine can give rise to more side-effects than other drugs.

Among proprietary remedies promethazine (Phenergan or Avomine) has been effective in single doses and to some extent also cyclizine hydrochloride (Marzine) and diphenhydramine and dimenhydrinate (Benadryl or Dramamine).

When the motion is mild, as happens on large liners, the advantages of hyoscine over other drugs may be less obvious than in the presence of sharp motion. American experiments on troopships were so designed that only long-acting drugs could have any effect and in these experiments meclozine hydrochloride 50 mg. (Ancolan, Bonamine, Sealegs, Postafene) which has a very long action was found best, followed by promethazine and cyclizine which are also long-acting drugs. It is difficult to assess the effects of drugs against motion sickness with complete objectivity on long journeys when the motion is comparatively mild, but it seems probable that under such conditions either hyoscine or cyclizine or promethazine might be satisfactory, whereas the balance of evidence now available would make the use of meclozine inadvisable.

REFERENCES

ARNER, O., *et al.* (1958) *Arch. int. Pharmacodyn.*, **117,** 404.
BAIN, W. A. (1952) *Lancet*, ii, 246.
BENNETT, R. A. (1928) *Brit. med. J.*, i, 752.
BETHELL, M. F. (1951) *Lancet*, ii, 888.
BORISON, H. L., and WANG, S. C. (1953) *Pharmacol. Rev.*, **5,** 193.
Brit. med. J. (1862) ii, 371.
Brit. med. J. (1952) ii, 553. Annotation.
Chem. and Drugg. (1959) **171,** 481. Leading article.
CHINN, H. I., *et al.* (1952) *Amer. J. Med.*, **12,** 433.
——, *et al.* (1953) *J. appl. Physiol.*, **6,** 257.
——, and SMITH, P. K. (1955) *Pharmacol. Rev.*, **7,** 33.
——, and OBERST, F. W. (1950) *Proc. Soc. exp. Biol., N.Y.*, **73,** 219.
ECCLES, J. C. (1953) The Neurophysiological Basis of Mind. Oxford; p. 193.
GAY, L. N., and CARLINER, P. E. (1949*a*) *Bull. Johns Hopk. Hosp.*, **84,** 470. (1949*b*) *Science*, **109,** 359.
GENEE, R. W. (1924) *Münch. med. Wschr.*, **71,** 166.
GIBSON, W. C., *et al.* (1944) *Proc. Ass. Comm. Aviat. Med.* Cited by Chinn and Smith (1955).
GLASER, E. M. (1952) *Lancet*, ii, 341.
—— (1953) *Brit. J. Pharmacol.*, **8,** 187.
—— (1955) *Int. Rec. Med.*, **168,** 23.
—— (1958) *Lond. Hosp. Gaz.*, Suppl. II.
——, *et al.* (1959) *J. Physiol.*, **146,** 152.
——, and HERVEY, G. R. (1951) *Lancet*, ii, 749.
——, —— (1952) *Lancet*, i, 490.
——, and MCCANCE, R. A. (1959) *Lancet*, i, 853.
——, and NEWLING, P. S. B. (1955) *Brit. J. Pharmacol.*, **10,** 429.
——, and WHITTOW, G. C. (1954) *Clin. Sci.*, **13,** 199.
——, —— (1957) *J. Physiol.*, **136,** 98.
GRUHLER, J. (1955) *Dtsch. med. Wschr.*, **80,** 108.
HANDFORD, S. W., CONE, T. E., Jr., CHINN, H. I., and SMITH, P. K. (1954) *J. Pharmacol.*, **111,** 447.
HASEGAWA, T. (1949) *Arch. Otolaryng., Chicago*, **50,** 708.
HILL, I. G. W., and GUEST, A. I. (1945) *Brit. med. J.*, ii, 6.
HILL, J. (1936) *Brit. med. J.*, ii, 802.
HOCKEN, T. M. (1861) *Lancet*, ii, 337.
HOLLING, H. E., *et al.* (1944) *Lancet*, i, 127.
IRWIN, J. A. (1881) *Lancet*, ii, 907.
Lancet (1843) ii, 531.
LEMON, A. E. (1919) *J. Amer. med. Ass.*, **73,** 104.
MCEVEDY, M. B. (1949) *Lancet*, i, 825.
MADDOCK, A. B. (1837) *Lancet*, i, 104.
MILLER, J. W., and GOODSON, J. E. (1958) U.S. Naval School of Aviation Medicine Reports. Randolph Field.
MONTO, R. W. (1947) *J. Mich. med. Soc.*, **46,** 114.
New and Nonofficial Drugs (1958) Philadelphia and Montreal; p. 34.
PAYNE, R. B., and HAUTY, G. T. (1953) U.S. Air Force School of Aviation Medicine Reports. Randolph Field.
——, and MOORE, E. W. (1955) *J. Pharmacol.*, **115,** 480.
PURKINJE, J. E. (1820) *Med. Jahrb. Wien*, **6,** 79. Cited by Chinn and Smith (1955).
Report on Study by Army, Navy, Air Force Motion Sickness Team (1956) *J. Amer. med. Ass.*, **160,** 755.
SHAW, C. C. (1954) *Milit. Surg.*, **114,** 347.
STRICKLAND, B. A., Jr., HAHN, G. L., and ADLER, H. (1950) *J. Aviat. Med.*, **21,** 90.
TYLER, D. B. (1946) *Amer. J. Physiol.*, **146,** 458.
WALSH, E. G. (1957) Physiology of the Nervous System. London, New York, Toronto; p. 219.
WILKS, S. (1875) *Lancet*, ii, 576.

DISCUSSION

Surg. Capt. W. Forbes Guild, R.N. (Portsmouth): I think we can say that Dr. Glaser has effectively taken the subject apart and put it together again. It is salutary for us, in this Section, to hear the truly academic approach, and then find it wedded to the practical. It surprises me, however, to find Dr. Glaser appearing to postulate a separate nerve pathway for nausea. Surely, this feature occurs when there is impediment to the completion of the circuit to initiate vomiting. Impediment further back can then be held to account for the headache which is so often the only symptom of motion sickness. If trials of this nature are to continue—and they necessarily involve the use of subjects on repeated occasions of exposure—would it be possible to work out and apply some factor for habituation?

There is a singular difference in the approach of the two sea-going services towards the allocation of accommodation. The Merchant Navy realizes that the optimum position is amidships, and sites its top accommodation accordingly. In the Royal Navy, the tradition is to subject the Admiral to the maximum linear acceleration by accommodating him right aft. Perhaps this is an unwitting support of Dr. Glaser's contention that increasing age lessens the susceptibility!

Major J. M. Adam, R.A.M.C. (London): It becomes clear before one has delved very deeply into the literature on motion sickness that the subject has tended to be bedevilled with a lack of adequate planning in the experimental approach. I should like, therefore, to associate myself with what Dr. Glaser has had to say about planning, and to underline his veiled plea for a clear enunciation of the object and a careful control of the variables in such experiments.

The Army has not been greatly troubled with this problem since the end of the late war. At that time it was fairly common to have 100% of troops in invasion craft affected by motion sickness. Now, however, with the increased use of aircraft, motion sickness is presenting itself once more in air-trooping and the movement of families by air, and particularly in troops of the strategic reserve, both airborne and parachute. The latter require special attention because of their specialist role as the "spearhead" of an operation, in which their importance may be out of proportion to their strength numerically.

The picture presented by parachute troops is not a clear one, and, although proportions of up to 30% may be affected in flight, the end-result is a combination of tension (before parachute jumping), lack of sleep, inadequate food, and fatigue from last-minute arrangements before emplaning, as well as motion sickness. Further, the side-effects of any remedy given to such troops must not affect the operational efficiency—the ability to land safely, to march long distances or to do battle immediately.

Wing Cdr. P. F. King (London): In the Royal Air Force, the management of motion sickness has to be considered in relation to, (*a*) aircrew, (*b*) the transport of airborne troops, and (*c*) the transport of casualties and passengers.

With aircrew, selection and training are of fundamental importance. Note should be taken of any history of susceptibility to motion sickness. While the labyrinth is the primary organ involved in motion sickness, turning tests, using the Bárány chair, are no longer used, as it has been shown that there is no relationship between the results of the Bárány chair test and the incidence of air sickness. Swing testing was first used in Russia in 1926, and much work has been done since then on this equipment—particularly during the 1939/45 War. It does not produce a motion exactly comparable to that inducing air sickness, and has not been adopted.

Air sickness comes early in training, but passes off rapidly as adaptation to the new motion develops. Adaptation is late in those in whom air sickness persists, and persisting pallor and headache after sickness indicate a poor prognosis in this respect.

In the past, there was some belief that air sickness was due to maladjustment to flying conditions, and a manifestation of psychiatric instability—but this is unlikely as animals are subject to motion sickness and under test conditions placebos have little effect. The very small number that fail to adapt are best removed from flying training. There is no place for the treatment of motion sickness by drugs in aircrew.

The transport of men, in whatever capacity, demands preventive measures and remedies in the management of motion sickness. The incidence of motion sickness in airborne troops is believed to be high and Park in 1942 noted an even higher incidence in glider-borne troops.

Casualties and other stretcher cases are frequently sedated, and are no problem. Ground airmen when travelling by air appear relatively immune to air sickness, except in the most turbulent conditions. The value and importance of a light pre-flight meal for aircrew and passengers cannot be overstressed.

Dr. G. Melvill Jones (Farnborough): Dr. Glaser suggested that motion sickness can be attributed in the main to a reflex originating in the utricular sensing elements of the vestibular apparatus. However, experience in the field of aviation suggests this is perhaps over-simplifying

the matter. For example, it is common to experience motion sickness, sometimes severe, when "flying" an aircraft simulator in which the cockpit remains stationary while a projected visual field behaves as it would in real flight. In this instance vision alone can be held responsible since no other sensory channel receives stimulation. Furthermore, one of the most provocative conditions in real flight occurs when exercising repeated rolling manœuvres, as when testing the rolling characteristics of an aeroplane. Here vestibular stimulation occurs, but is largely confined to the rotation sensing elements, namely the semicircular canals, rather than the utricle. In this connexion it is also well known that experiments involving pure rotation, as in a rotating chair, are capable of inducing severe motion sickness after a very short exposure.

Observations such as these tend to support the contention that motion sickness arises when there is conflict between orientation cues derived from different sensing elements, rather than as the result of a simple reflex derived from the utricle, and it would be interesting to hear Dr. Glaser's views on this point.

The President: The problem of motion sickness is of great importance to all the Services, particularly in wartime when it is essential to keep personnel fighting fit during transport and especially on disembarkation, whether from landing craft, gliders or other forms of transport aircraft. In the prevention of motion sickness under such conditions, Dr. Glaser's experiments and observations have shown convincingly that hyoscine hydrobromide still holds pride of place among the anti-motion-sickness drugs available at present. This gives support to the policy of the R.A.F. and the British civil airlines, who have found in practice that hyoscine was and still is the medicament of choice. I feel, however, that cyclizine requires to be investigated further.

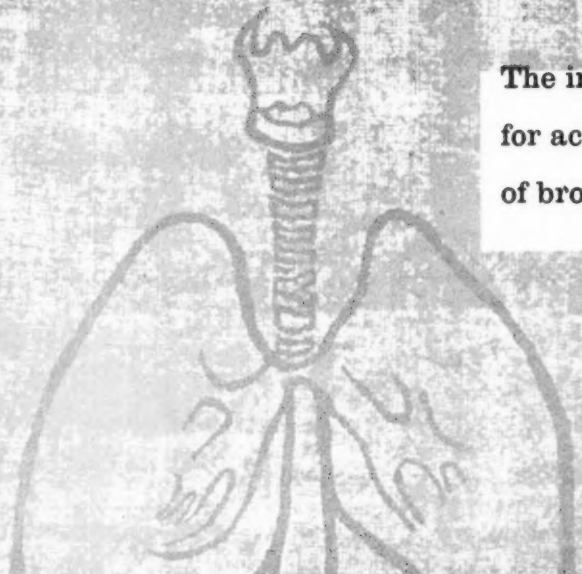
The incidence of air sickness among passengers in civil airliners which nowadays fly above or around "bad weather" is no greater on an average than 1%, though in monsoon conditions the incidence may at times be 10% or more, if anti-motion-sickness drugs have not been given. In troop-carrying aircraft, especially in the case of paratroops prior to a jump, air sickness may affect the majority, but here there is a strong psychological element. It is important to assess not only the anti-vomiting effects of the drugs used, but also to assess their effect on fighting efficiency. Is it not better to let a man be sick and have done with it, than to prevent vomiting and leave him with a nausea hangover?

As regards habituation to motion, it is interesting to note that in the R.A.F. during the war some 17% of trainees were air sick on their first training flight, 4% on their second, and 0·5% frequently after that, and these had to be taken off flying. These airmen were a selected group submitted to strenuous elimination tests before final selection for training.

Dr. Glaser in reply: Surgeon Captain Forbes Guild was certainly right in suggesting that a "habituation factor" might be useful, but we still know too little about habituation even to predict whether such a factor could be obtained. I am grateful to Major Adam for stressing the importance of properly conducted experiments, since badly conducted ones are continually being quoted in support of unsatisfactory drugs. I was interested also by his remark that so many paratroops are sick before jumping, but I suspect that fewer men would be affected if they were given 0·6 to 1·0 mg. of hyoscine hydrobromide one hour before take-off, while their efficiency would not be impaired by this.

I tried to avoid saying too much about nervous mechanisms in motion sickness, but Surgeon Captain Forbes Guild may be right in what he said about nausea. Yet, I should have thought that relaxation of the stomach might explain nausea, as it is the first stage of the reflex response and it begins before there is any vomiting. I am glad that Dr. Melville-Jones drew attention to impulses arising elsewhere than in the utricle and I might add that the response can be reinforced by further stimuli from muscle proprioceptors, the olfactory epithelium, and perhaps also by viscероceptors. Impulses originating in the brain itself must have both facilitatory and inhibitory influences, though I agree with Wing Commander King that the importance of psychological factors can be exaggerated. One central nervous factor which is often disregarded is that, in the absence of a conditioned reflex, the stimuli for motion sickness must always be present for a time of the order of minutes and sometimes of the order of hours before a response can take place. This means that an immense amount of sensory information must be stored by the brain before nausea or vomiting can begin. The interruption of reverberating neuronal circuits which store information may indeed be the process by which drugs and habituation prevent motion sickness.

I am glad that the question was asked by Colonel Grey Turner about dangling a chain from a motor car. This will certainly reduce static electricity in the car, but whether it will prevent motion sickness is another question. Yet, if vitriol and red herrings have been successful, why not a chain?



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President—J. R. WHEELER, F.R.C.S.

Meeting
February 12, 1959

A paper entitled **Current Work on Auto-immunity in Relation to Orbital Disease** was read by Mr. BARRIE R. JONES (*see* JONES, B. R., 1958, *Lancet*, ii, 773).

Meeting
May 14–16, 1959

MEETING WITH THE IRISH OPHTHALMOLOGICAL SOCIETY IN BELFAST

JAMES CRAIG LECTURE

Enzymatic Zonulolysis

By JOAQUÍN BARRAQUER
Barcelona, Spain

INTRODUCTION

THE discovery of the action of alpha-chymotrypsin on the human zonule (enzymatic zonulolysis) in June of 1957 [1] introduced a fundamental change in the surgery of the lens. In this paper our personal experience with enzymatic zonulolysis from January 1958 to February 1959 is described, involving operations on 297 eyes from patients of all ages. The 297 cases are divided into *two series*. *The first series* comprises those cases treated surgically from January to July 1958 employing the surgical technique evolved in our experimental work. *The second series* comprises those cases treated surgically from September 1958, but with technical modifications.

FIRST SERIES (JANUARY TO JULY 1958)

The first series consisted of 195 cases of total lens extraction in patients from 1 to 90 years of age suffering from cataract or high myopia. The technique employed was that of classical phakoerysis [2, 4] applying alpha-chymotrypsin behind the iris through the pupil and the peripheral iridectomy.

The results, taken as a whole, were satisfactory. Total lens extraction was attained in all cases using a 1/5,000 solution (in 7 cases, in spite of capsular rupture at the end of the extraction, the lens could be totally removed). The following complications occurred, which were exceptional in our series of cataracts extracted without the use of the enzyme [3]: delay in formation of the anterior chamber; flattening of the anterior chamber; development of anterior synechiæ; iris prolapse; epithelial downgrowth (Table I). The majority of these complications affected patients over 60 years of age, in whom the classical intracapsular method (without enzyme) gives excellent results.

TABLE I.—FIRST SERIES—JANUARY TO JULY 1958—195 CASES (AGES FROM 1 TO 89 YEARS) COMPLICATIONS

Ages	20–89	10–19	1–9
No. of cases	170	13	12
Ineffectiveness of alpha-chymotrypsin	2		
Vitreous loss	1	2	2
Delayed formation of anterior chamber	3		
Flattening of anterior chamber 10/20 days	8		1
Anterior synechiæ with hypertension	3	2	
Prolapse of iris	3		
Incision partially open. No prolapse of iris	3		
Striate keratitis of 10/20 days' duration	4		
Epithelial downgrowth anterior chamber	1		
Retinal detachment	3	2	

Subconjunctival filtration through the incision without further complication, was also commoner than in operations without alpha-chymotrypsin. (Figs. 1, 2, 3 and 4).

The most serious complications arose in 10 cases with corneal incisions: 1 case of epithelial downgrowth, 2 of the 3 cases of iris prolapse, 4 cases of prolonged striate keratitis and 3 cases of late gaping of the incisions.

All this led us to consider the possibility of some noxious effect of the alpha-chymotrypsin on the healing of wounds. Delay in formation of the anterior chamber could be explained on similar grounds. The formation of anterior synechiæ could also be due to the same mech-

anism (filtration with occlusion of the wound by the iris root), or to a chemical or mechanical irritation of the iris by anterior chamber irrigation. This interpretation led us to modify our technique.

Second Series
(September 1958 to February 1959)

As these complications appeared more frequently in elderly patients, zonulolysis was not employed on patients over 60 years of age in the second series except when undue capsular fragility was suspected. In patients under 10 years of age in this series serious complications arose, so that the use of zonulolysis was abandoned, as will be explained later.

The following modifications in technique were tried out:

Alpha-chymotrypsin.—With the object of reducing the secondary effects to a minimum, we tried the solution in 1/10,000 dilution in certain cases. An increase of capsular ruptures occurred (all those appearing in the period September 1958 to February 1959, Table IV, Cases C, J, M, N), whereas small subconjunctival filtrations appeared similar to those found when using the 1/5,000 solution. Other complications which we were trying to eliminate continued to appear (Table IV, Cases I, Q).

It was concluded that employment of the 1/10,000 solution was of no advantage and reduced the percentage of total extractions.

Alpha-chymotrypsin inhibitors.—In 6 cases we employed betaphenylpropionic acid in the form of anterior chamber irrigations to inactivate the chymotrypsin; in 1 of these cases, however, there was delayed formation of the anterior chamber while in 2 cases discrete subconjunctival filtration took place.

We do not consider the use of inactivators advantageous, because their addition represents another operative procedure. It was decided to continue irrigating with physiological saline solution to wash out the remainder of the ferment once zonulolysis was obtained.

Incision.—With the idea of securing a more active cicatrization and an immediate hermetic closure, we have systematically employed in our second series a more scleral incision with conjunctival flap which completely covers the sectioned area.

This technique has proved of great security, no incision having partially opened since its introduction. The effectiveness of this incision was demonstrated by the absence or rapid disappearance of striate keratitis, contrary to what occurs sometimes with corneal incisions.

Extraction.—In some cases we have used the Smith method which has the advantage of not requiring the introduction of an instrument for the extraction, thus reducing the operative trauma (Paufique).

We still consider the erysiphake extraction method to be the best in the majority of cases.

Medication.—With the object of avoiding any inflammatory reaction, we systematically administer small doses of anti-inflammatory steroids and antihistamines during the first days following surgery.

Rest in bed with binocular dressing for three days is part of the post-operative care, followed by a monocular dressing and relative rest for eight more days. Up to twenty days following surgery the patient ought to use a plastic protector during the night.

Results

In order to show the results obtained in this second series, we have classified the 102 cases in three groups according to ages:

Group 1, from 20 to 79 years: 83 cases (Tables II, III, IV).

Group 2, from 10 to 19 years: 9 cases (Table V).

Group 3, from 1 to 9 years: 10 cases (Table VI).

We have not employed alpha-chymotrypsin in patients over 80 or under 1 year old.

Table II.—Second Series, First Group—September 1958 to February 1959—83 Cases (Ages from 20 to 79 Years) Ages and Diagnosis

Ages Years	Diagnosis	
20–29	Congenital cataract (mature)	1
	Congenital cataract (immature)	1
	Traumatic cataract	1
	Symptomatic cataract	1
	High myopia	10
30–39	Intumescent senile cataract	1
	Symptomatic cataract	2
	Clear lens in high myopia	6
	Traumatic cataract	2
40–49	Immature senile cataract	3
	Intumescent senile cataract	1
	Myopic cataract	3
	Cataract and glaucoma	2
	Clear lens in glaucoma	1
	Clear lens in high myopia	9
	Subluxated lens	1
50–59	Mature senile cataract	1
	Immature senile cataract	3
	Intumescent senile cataract	2
	Myopic cataract	15
	Cataract and glaucoma	1
	Clear lens in high myopia	3
	Diabetic cataract	1
60–69	Mature senile cataract	4
	Intumescent senile cataract	2
	Myopic cataract	3
70–79	Mature senile cataract	2
	Cataract and glaucoma	1

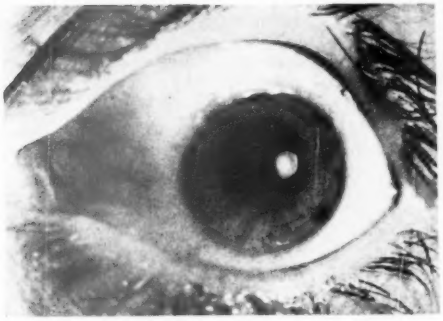

FIG. 1.—An eye with subconjunctival filtration. Both the depth of the anterior chamber and the tension are normal.

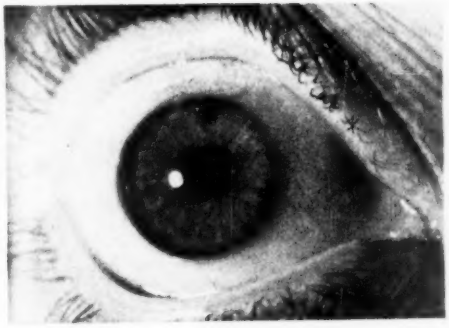

FIG. 3.—The same eye twenty days later. The filtration has disappeared.

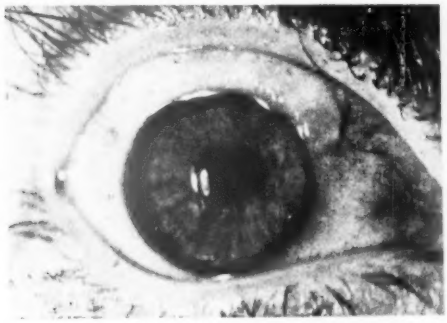

FIG. 2.—Extensive subconjunctival filtration which subsided within twenty days.

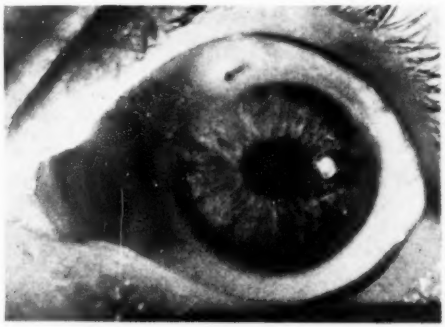

FIG. 4.—Another eye with persistent subconjunctival filtration. The appearance of the cicatrice is that of Elliot trephining. Anterior chamber and tension normal.

Group 1 (83 *cases*).—The results have been uniformly excellent.

Visual acuity varied between 0·2 and 1 in 72 cases as detailed in Table III. In 8 cases the improvement was not greater than 0·1 due to old retinal lesions.

In 1 case (G), V.=0·1 (R.D. cured); in 1 case (D), vision remained at light perception only due to total retinal detachment; in 1 case (N), blindness ensued due to severe hyphæma and phthisis bulbi.

The *operative incision* is invisible in the majority of cases thirty days after the operation. Subconjunctival filtration appeared in 20 cases without delay in formation or flattening of the anterior chamber. In 16 cases this filtration was negligible and disappeared spontaneously within a few days. In 4 cases, thirty days after the operation a subconjunctival bleb of aqueous humour continued to exist, but ocular tension was normal. In one case only (Table IV, Case R, Figs. 5 and 6), in which the incision was entirely

TABLE III.—SECOND SERIES, FIRST GROUP—SEPTEMBER 1958 TO FEBRUARY 1959—83 CASES (AGES FROM 20 TO 79 YEARS)
VISUAL RESULTS

	Visual acuity									
	From 0·01 to 0·1	0·2	0·3	0·4	0·5	0·6	0·7	0·8	0·9	1
No. of cases (senile, traumatic, symptomatic cataracts, &c.)	5	2		1	2	5	4	2	3	7
No. of cases (clear lens in high myopia and myopic cataracts)	6	3	9	4	13	4	7	3	1	2

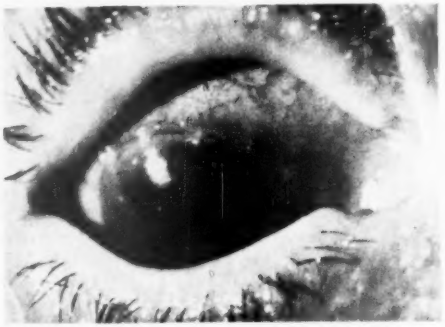

FIG. 5 (*Case R*).—Striate keratitis (incision without flap).

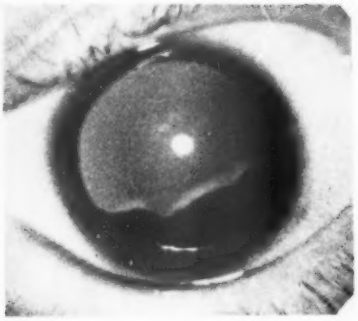

FIG. 7 (*Case C*).—Subluxation and lens coloboma with high myopia.

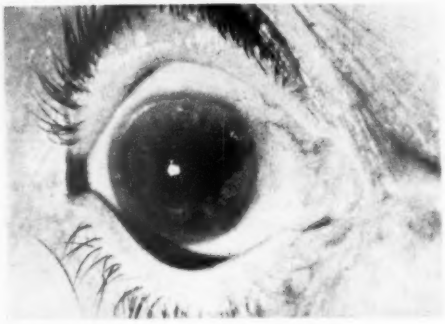

FIG. 6 (*Case R*).—The same eye after treatment. The keratitis has disappeared.

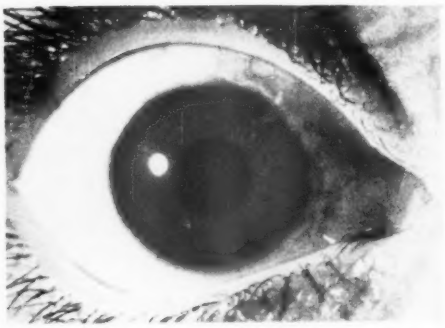

FIG. 8 (*Case C*).—Result after extraction.

corneal, striate keratitis appeared in intense form but it yielded to 15 days' infra-red treatment. The cornea was slightly opened at the incision in its superficial layers without filtration.

The pupil was round and central in all cases except in four (anterior synechiæ, Table IV, Cases A, D, O, Q). In 3 cases the iridectomy was total (in 2, previous iridectomy for iridocyclitis; in 1, iridectomy for pupillary rigidity, Case P).

The iris presented no anatomical or functional alterations except in 3 cases in which various grades of atrophy secondary to other complications arose (Cases A, D, N).

We have not seen any noteworthy pigment liberation as described by others.

The anterior chamber angle remained normal except in 4 cases (A, D, O, Q), in which anterior synechiæ appeared. In 3 cases of persistent subconjunctival filtration a small endothelial gap remained in the incision.

The anterior limiting membrane of the vitreous humour remained intact in 77 cases. Delayed rupture appeared in 3 cases and in 3 others (B, D, P) it occurred at operation.

The ocular tension measured with the aplanation tonometer twenty days after the operation was normal in all cases (readings between 10 and 20 mm.Hg). In the cases affected with preoperative glaucoma the tension remained controlled. In 2 cases (D, G) persistent hypertension appeared in connexion with other complications.

Complications have been reduced to a minimum and in only 2 cases (D, N) have the results been unfortunate. They are summarized in Table IV and the most interesting are as follows:

A.—Delay in anterior chamber formation was due to block of the pupil and of the peripheral iridectomy

TABLE IV.—SECOND SERIES, FIRST GROUP—SEPTEMBER 1958 TO FEBRUARY 1959—83 CASES (AGES FROM 20 TO 79 YEARS)
COMPLICATIONS

Ages	Diagnosis		Ineffectiveness of alpha-chymotrypsin	Capsular rupture	Hyaloid rupture with vitreous loss	Hyaloid rupture without vitreous loss	Subluxated lens	Hyphæma	Delayed anterior chamber formation	Flattening of anterior chamber	Anterior synechiæ	Iris prolapse	Iridocyclitis	Striate keratitis of 10 to 20 days' duration	Secondary hypertension	Retinal detachment
20–29	Congenital cataract ..	1 (A)														
	Symptomatic cataract ..	1 (B)				B			A		A					
	Traumatic cataract ..	1 (C)		C												
30–39	High myopia	1 (D)			D				D		D				D	D
40–49	Immature senile cataract ..	1 (E)								E						
	Intumescent senile cataract	2 (FG)	F										G		G	G
	Cataract and glaucoma ..	1 (H)								H						
	High myopia	1 (I)							I							
50–59	Intumescent senile cataract	1 (J)		J												
	Myopic cataract	4 (KLMN)	L	M N				N								K
	High myopia	1 (O)									O					
60–69	Mature senile cataract ..	2 (PR)				P	P							R		
	Intumescent senile cataract	1 (Q)									Q	Q				

NOTE.—The letters in brackets in the diagnostic column correspond with the same letters in the complication columns and refer to one eye of the patient. A letter repeated in several complication columns indicates therefore that the complications refer to *one and the same eye* (consequences of previous complications).

(air in anterior chamber). Another peripheral iridectomy was made below. Peripheral synechiæ remained which deformed the pupil. Amblyopia.

C.—Foreign body in the lens. Irrigation with 1/10,000 solution of alpha-chymotrypsin. Capsular fragment remained behind the iris.

D.—High myopia with large sclero-choroidal lesions. Immediately after making the incision, the lens protruded and soon after application of the chymotrypsin was expelled with vitreous loss. There was no formation of the anterior chamber due to block of the pupil and of the peripheral iridectomy with solid vitreous humour. Air injected. Secondary glaucoma. Posterior sclerotomy with peripheral iridectomy was performed. Thirty days later there was a fresh rise in tension due to extensive peripheral synechiæ. Cyclodialysis. Hypotony. Total retinal detachment (T.R.D.).

E.—Partial loss of anterior chamber due to unknown causes. Spontaneous recovery after four days.

F, L.—Alpha-chymotrypsin was ineffective at 1/10,000 due to the presence of vitreous fluid in anterior chamber before making the irrigation.

G.—Incomplete Marfan syndrome. Hypertensive iridocyclitis. Hypotension. R.D. Cured with lamellar scleral resection (L.S.R.).

H.—Loss of anterior chamber due to choroid detachment (C.D.). Cured in eight days with medical treatment.

I.—Delay in anterior chamber formation due to subconjunctival filtration of the incision. Formation in three days upon dilating the pupil.

J.—Capsular rupture upon passing the lens through poorly dilated pupil (alpha-chymotrypsin 1/10,000).

K.—Retinal detachment one month after the operation without trauma, and with an intact vitreous face. Under treatment with L.S.R.

N.—Large myopic lesions. Hypertensive vascular sclerosis. A deep-seated vessel of the scleral incision bled intensely; galvanocauterization. Capsular rupture (alpha-chymotrypsin 1/10,000). Six hours after the operation, total hyphæma with hypertension simulating expulsive hæmorrhage. Slow reabsorption. Hypotony. Phthisis bulbi.

O.—Anterior synechia without previous pathology. Pupil deformation.

P.—Pupil rigid and poor dilatation made extraction difficult. Lens subluxation provoked upon second application of erysiphake. Extraction easy with total iridectomy and scoop. Vision—0·8, No. 1.

Q.—Obstruction of the pupil and of the peripheral iridectomy which provoked hypertension and several small subconjunctival iris prolapses. Inferior peripheral iridectomy was performed which re-established communication between the posterior and anterior chambers with spontaneous reduction of the iris prolapses, leaving only a small anterior peripheral synechia which deformed the pupil.

Group 2 (9 *cases*).—The functional results were

TABLE V.—SECOND SERIES, SECOND GROUP—SEPTEMBER 1958 TO FEBRUARY 1959—9 CASES (AGES FROM 10 TO 19 YEARS)
COMPLICATIONS

Ages	Diagnosis		Ineffectiveness alpha-chymotrypsin	Vitreous loss	Delayed anterior chamber formation	Secondary glaucoma
10–19	Subluxated lens ..	4 (*ABCD*)	*D*	*ABCD*		
	Traumatic cataract ..	1 (*F*)				
	Symptomatic cataract	1 (*H*)				
	High myopia ..	3 (*EGI*)		*EI*	*E*	*E*

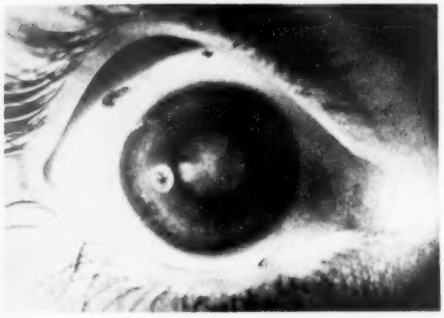

FIG. 9 (*Case F*).—A case of traumatic cataract with a foreign body in the lens.

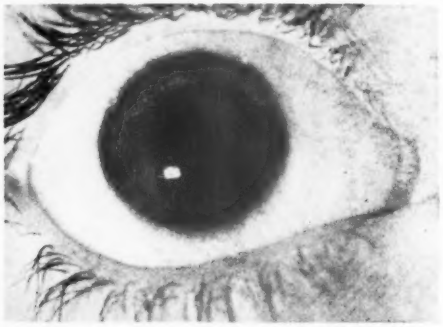

FIG. 10 (*Case F*).—Perfect extraction by Smith's method. The patient is 16 years old.

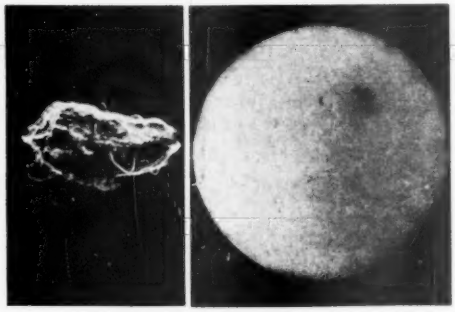

FIG. 11 (*Case F*).—The lens is intact and the foreign body can be seen close to the posterior capsule at the 1 o'clock position. At the left, the foreign body after its extraction for examination.

similar to those of group 1. The operative technique is difficult because there is a tendency towards prolapse of the vitreous humour, particularly in high myopia. This may be due to a higher scleral elasticity.

The complications are summarized in Table V while the results are given below:

A.—Subluxated traumatic cataract, 10 years of age. Vitreous forward. Lens extraction with vitreous loss. Air was inserted into anterior chamber and the pupil was rounded by means of a spatula. Perfect anatomical result. Old atrophy of the optic nerve.

B.—Ectopia lentis (Marfan), 14 years of age. Vitreous forward. Air used. Round pupil. Vision = 0·8, No. 1.

C, D.—Lens coloboma with subluxation and high myopia of both eyes, 12 years of age. Left eye: alpha-chymotrypsin was ineffective due to the presence of vitreous humour. Zonulolysis effective in right eye with the precautions and special technique to be mentioned later (Figs. 7 and 8). Air. Round pupil. Vision right eye = 0·6, No. 1; vision left eye = 0·5, No. 1.

E.—High myopia. 12 years of age. Loss of vitreous body. Delay in formation of anterior chamber due to blockage of the pupil and of the peripheral iridectomy. Peripheral iridectomy again performed; pupil distorted. Vision = 0·4, No. 1.

F.—Traumatic cataract with foreign body in the lens. 16 years of age. No air. Round pupil. Vision = 0·9, No. 1 (Figs. 9, 10 and 11).

G.—High myopia. 16 years of age. Air. Round pupil. Vision = 0·6, No. 1.

H.—Secondary cataract, 17 years of age. Air. Round pupil. Perfect anatomical result (long-standing total retinal detachment).

I.—High myopia. 17 years of age. Vitreous loss upon closing suture. Total iridectomy. Air. Vision = 0·4.

Group 3 (10 *cases*).—The good results and few complications of our first series encouraged us to employ alpha-chymotrypsin in young patients. However, in the second series, serious complications have been the rule and although they could be avoided in the majority of cases by special techniques, we believe that total lens

TABLE VI.—SECOND SERIES, THIRD GROUP—SEPTEMBER 1958 TO FEBRUARY 1959—10 CASES (AGES FROM 1 TO 9 YEARS)
COMPLICATIONS

Ages	Diagnosis	Vitreous loss	Delayed anterior chamber formation	Anterior synechiæ	Iris prolapse	Secondary glaucoma
1-9	Mature congenital cataract .. 2 (*ce*) Immature congenital cataract 7 (*ijadfhb*) Subluxated lens .. .. 1 (*g*)	*e* *ij* *g*	*ce* *adfh*	*abij*	*c* *df*	*e* *d*

NOTE.—The letters in brackets in the diagnostic column correspond with the same letters in the complication columns and refer to one eye of the patient. A letter repeated in several complication columns indicates therefore that the complications refer to *one and the same eye* (consequence of previous complications).

extraction in this group ought to be reserved for experimental cases. We were unable to account for the difference of results between the first and second series.

The complications that occurred in this group are shown in Table VI and the details are specified below:

a.—Anterior nuclear polar cataract, 2 years of age: air in anterior chamber. Hypertension due to block of the pupil and of the peripheral iridectomy which delayed anterior chamber formation. Formation of extensive peripheral synechiæ. Peripheral iridectomy and posterior sclerotomy again required. Tension remained normal with a distorted pupil (Fig. 12). Vision useful.

b.—Posterior capsular and nuclear cataract, 3 years of age: air in anterior chamber: formation of extensive anterior synechiæ; hammock pupil; vision useful.

c.—Mature congenital cataract. 3 years of age: zonulolysis difficult but effective upon repeated irrigations. Air in anterior chamber; block of the pupil and peripheral iridectomy with delay in anterior chamber formation. Prolapse of iris. Resection and posterior sclerotomy. Hammock pupil. Vision useful.

d.—Anterior polar nuclear cataract: 3 years of age. Air in anterior chamber: pupillary block with delay in anterior chamber formation and prolapse of iris. Secondary glaucoma. Prolapse abscissed: hammock pupil and staphyloma in the incision zone. Vision bad.

e.—Monocular cortinuclear cataract (amblyopia). 5 years of age. Vitreous loss; total iridectomy; air. Partial opening of the incision requiring new suture. Secondary glaucoma. Vision bad.

f.—Anterior capsular cataract, 7 years of age. Air. Delay in anterior chamber formation wth prolapse of iris: prolapse abscissed: posterior sclerotomy and peripheral iridectomy below. Hammock pupil. Vision 0·4, No. 1.

g.—Subluxated lens with coloboma: 7 years of age: vitreous prolapse previous to extraction. Effective zonulolysis; air; hammock pupil; vision 0·2, No. 3.

h.—Cortinuclear cataract; microcornea; 9 years of age. Lens aspirated by erysiphake. Air. Delay in anterior chamber formation due to block of the pupil and of the peripheral iridectomy. Inferior peripheral iridectomy necessary. Round pupil. Vision 0·2, No. 3.

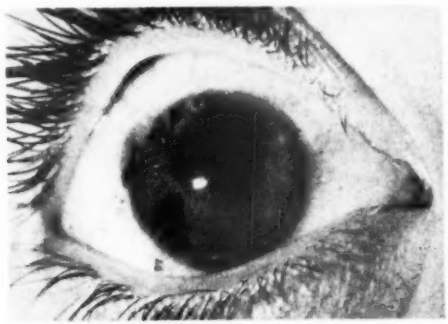

FIG. 12 (*Case a*).—Distortion of the pupil due to hypertension and anterior synechiæ. Another peripheral iridectomy is performed below.

i.—Monocular posterior capsular cataract (amblyopia); 9 years of age: vitreous loss. Air in anterior chamber. Extensive peripheral synechiæ with atrophy of iris. Distortion of the pupil. Vision 0·1, No. 8.

j.—Monocular posterior lenticonus (amblyopia). 9 years of age. Vitreous loss. Air. Peripheral synechiæ with atrophy of iris. Round pupil. Vision = 0·03, No. 9.

Our experience with enzymatic zonulolysis acquired during the last fourteen months and described above allows us to give precise indications for its use and to recommend the technique of choice.

Indications

(1) *Diagnosis.*—All types of cataracts. Transparent lenses (high myopia, 20 dioptres; angle-closure glaucoma).

(2) *Age.*—In patients over 20 and up to 60 years of age, the systematic use of enzymatic zonulolysis is advisable. In patients of more than 60 years, it may be omitted, being indicated in intumescent cataracts, in high myopia and always when a greater zonular than capsular resistance is suspected. In adolescents of 10 to 20 years, an experienced surgeon can obtain good results, although it must be pointed out that the intervention is difficult. In patients less than 10 years old, intervention should be confined to experimental cases only.

(3) *Pupil dilated* (8 mm.) with Neosynephrine (Neophryn) 10%. We now advise dilatation of the pupil, contrary to our previous publications, because chamber irrigations frequently tend to contract the pupil.

(4) *Incision.*—Corneoscleral conjunctival. The incision must be made so that its borders are regular to ensure better coaptation; it should lie in a vascular area to encourage rapid cicatrization, and once the suture is made, it should be covered by a conjunctival flap because *immediate and complete hermetic sealing* of the anterior chamber is of the utmost importance.

The topography of the incision necessitates careful hæmostasis of its scleral borders. The surest, quickest and least traumatic method consists of irrigation of the incision with physiological saline to localize the bleeding points and coagulate them with precision by the use of fine galvanocautery.

It must be wide (180 to 200 degrees) to facilitate surgical intraocular manœuvres and to reduce trauma to the corneal endothelium to a minimum. This wide incision increases the necessity of perfect closure.

(5) *Peripheral iridectomy*, small and basal.

(6) One *suturing stitch*, corneoscleral at twelve o'clock position.

(7) *Irrigation* with 1/5,000 solution of alpha-chymotrypsin. A precision syringe is used, having a smooth plunger and a silver cannula

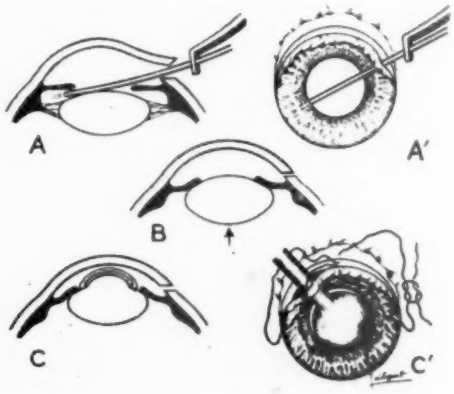

FIG. 13.—Technique of irrigation with alpha-chymotrypsin (A and A¹). In B it is seen that the lens after liberation from the zonule becomes globular and rises, showing a tendency to prolapse. Application of the suction cup (C and C¹).

Technique

(1) *Preparation of the alpha-chymotrypsin solution.*—1/5,000 concentration. Lower concentrations are often inefficient. Room temperature or about 37° C. Activity of ferment increases with increase in temperature of solution, but its stability diminishes, that is to say, it loses activity quicker. The solution must be freshly prepared as it loses activity within a few hours. The syringe and cannula must be sterilized in dry heat as any residue of alcohol or detergents left in the syringe or cannula after sterilization with these agents will inactivate the ferment.

(2) *Anæsthesia.*—We prefer general anæsthesia potentiated with curare.

with rounded and polished borders (an ordinary cannula may easily damage the iris or lens).

In order to control the movements of the cannula within the ocular globe, the syringe should be held in the right hand, while its base is steadied with forceps held in the left hand.

The cannula should penetrate the posterior chamber between the iris and the lens, passing through the pupil to irrigate the zonule (Fig. 13). It is convenient to depress the lens with the cannula to avoid damaging the pigmentary layer and liberating its pigment. This depression should be very light and gentle, in order not to damage the capsule nor luxate the lens. A total of 2 ml. of the solution should be injected gently into the four quadrants. Then the conjunctiva and incision borders should be washed with physiological saline while the anterior chamber is held closed by means of the forceps. Finally, the anterior chamber is washed with physiological saline solution, Ringer's solution, Hank's solution, penicillin, &c., to remove the remains of the ferment once it has completed its mission (1 to 2 minutes).

(8) *Lens extraction.*—Preferably with the erysiphake, for in that way it is not necessary to exert any pressure upon the lens when extracting it (Fig. 13).

Tumbling facilitates separation of the posterior surface of the lens from the vitreous. The corneal wound is held wide open to verify this separation as well as the integrity and hypotony of the vitreous humour. Moreover, this manœuvre has the advantage of reducing friction against the corneal endothelium to a minimum.

If during the version we discover a capsular-hyaloid adhesion, this may be liberated with the posterior surface of the cornea, making counter-pressure with the forceps. The same should be done if the vitreous tends to prolapse.

(9) *Irrigation with* 1/10,000 *acetylcholine solution* to contract the pupil.

(10) Multiple corneoscleral subconjunctival *sutures* which guarantee hermetic and safe closure of the incision. The natural silk (dyed with methylene blue) permits the use of 7 to 14 corneoscleral stitches without producing inflammatory reaction. The stitches are covered with conjunctiva so that the closure of the incision is hermetic.

(11) Fixing of the conjunctival flap with plasma-thrombin solution or, if that is not available, two conjunctival stitches may be inserted.

(12) The anterior chamber is left full of physiological saline solution or sterile air if necessary.

(13) Subconjunctival injection of cortisone and application of pilocarpine ointment.

Conclusions

From the study of our 297 cases of intracapsular lens extraction by means of enzymatic zonulolysis, and from the communications received from other authors, it can be seen that:

(1) Alpha-chymotrypsin in aqueous solution at 1/5,000 is highly efficient for destroying the zonular fibres or their union with the lens.

(2) No secondary effects of importance appear if the aforementioned precautions are observed.

(3) In cases of degenerated vitreous humour it is absolutely necessary to avoid contact of vitreous and zonule in order to allow the alpha-chymotrypsin to act effectively. In these cases the use of a Flieringa ring is recommended because it avoids collapse of the globe.

(4) The greater incidence of subconjunctival filtration which is generally transitory and without subsequent complications makes one suspect a delay in the corneo-endothelium cicatrization where alpha-chymotrypsin has been used. This is of no importance and will not occur if the operative technique that we have recommended is observed.

(5) It is advisable to avoid air injection into the anterior chamber as it may produce block of both the peripheral iridectomy and the pupil with secondary complications. It should be injected only in cases of vitreous loss in combination with section of the prolapse and its reduction by means of a spatula.

(6) In cases of traumatic cataract or where a very fragile lens capsule is suspected, Smith's manœuvre for intracapsular extraction is to be preferred (Figs. 9, 10 and 11).

(7) Our wide personal experience (297 cases) allows us to affirm that the complications mentioned by some authors (intense striate keratitis, liberation of iris pigment, rupture of the vitreous face, secondary glaucoma, &c.) are not directly related to the use of alpha-chymotrypsin and they can be readily avoided by the employment of a proper operative technique.

REFERENCES

1 Barraquer, J. (1958) Enzymatic zonulolysis—contribution to lens surgery. Preliminary note. Real Academia de Medicina de Barcelona (Spain).

2 Barraquer, I. (1956) Evolution of phakoerysis. Internat. Course in Ophthalmology, Vol. I. Instituto Barraquer, Barcelona (Spain).

3 Barraquer, J. (1957) Conclusions deduced from the study of our statistics of cases of operations for phakoerysis, year 1956. *Estud. Inform. oftal.*, **8**, 25. Instituto Barraquer, Barcelona (Spain).

4 ——, and Boberg-Ans, J. (1959) *Brit. J. Ophthal.*, **43**, 69.

The following papers were also read:

Ophthalmology in the South Pacific.—Mr. J. R. WHEELER.

Retrobulbar Neuritis.—Presidential Address to the Irish Ophthalmological Society by Mrs. B. H. LYNN.

Modern Trends in Disseminated Sclerosis.—Dr. R. S. ALLISON.

The Effect of Neptazane on Intra-ocular Pressure in Relation to its Systemic Action and its Clinical Application.—Dr. DOROTHY A. CAMPBELL.

A Critical Analysis of the Results of Lacrimal Surgery in over 200 Cases.—Mr. B. W. RYCROFT.

Trends in Ophthalmological Thought.—Somerville-Large Lecture by Dr. G. P. CROOKES.

Cataract Glaucomatosa.—Mr. BARRIE JONES.

Light Coagulation Therapy.—Mr. L. G. FISON and Mr. G. W. BLACK.

The paper by Dr. Campbell will be published in the *British Journal of Ophthalmology;* the other papers will appear in the *Transactions of the Ophthalmological Society of the United Kingdom.*

Meeting
June 11, 1959

A CLINICO-PATHOLOGICAL meeting at which the following cases were shown:

Persistent Hyperplastic Vitreous.—Mr. D. P. GREAVES and Dr. D. R. BARRY.

Temporal Arteritis.—Dr. J. F. CULLEN (for Mr. J. M. L. HOWAT) and Professor N. ASHTON.

Necrotizing Granulomatosis of Orbit [Wegener's Granulomatosis].—Mr. E. S. PERKINS (for Mr. A. R. WEAR) and Dr. E. B. LA BROOY.

Chronic Endophthalmitis.—Dr. C. R. FENTON (for Mr. F. RIDLEY) and Professor N. ASHTON.

Pseudo-exfoliation of Lens Capsule.—Mr. C. COOK and Dr. W. S. HUNTER.

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Section of Neurology

President—HUGH GARLAND, T.D., M.D., F.R.C.P.

Meeting
May 7, 1959

DISCUSSION ON THE TREATMENT OF INTRACTABLE PAIN

Dr. W. Ritchie Russell (Oxford):

Though the importance of the posterior nerve roots for the conduction of sensation was demonstrated by Charles Bell early in the last century, it is easy to forget that little more than half a century has passed since the neuron theory of the structure of the central nervous system became widely accepted.

In recent decades the increased knowledge of the physiological, anatomical and chemical responses of neurons has necessitated a re-appraisal of the clinical approach to pain, and this symposium will, I hope, provide some clarification of the subject.

There is little time to consider drugs, but in recent years the value of tranquillizers to relieve apprehension and of amphetamine or Ritalin to relieve depression has added considerably to the methods available to counter the personal reaction to pain which so often needs treatment.

If we put aside for the time being the question of drug treatment, we can approach the problem of intractable pain simply with the idea of blocking conduction to the C.N.S. by dividing peripheral nerves, or tracts in the spinal cord or brain-stem, and if this is not successful, with destruction of the prefrontal lobes. This approach is at first sight quite straightforward and rational, but modern knowledge of C.N.S. activity suggests many alternatives.

In the first place it should be emphasized that the amount of distress caused by intractable pain is a personal matter, and indeed seems to be an acquired characteristic of the individual. This characteristic is probably determined by the attitude of the parents in infancy to painful episodes, from which we might conclude that all patients who suffer much as a result of pain have been badly brought up from this point of view.

However true this may be, it does not help our problem very much except in so far as emotional thoughts, say of fear in relation to the pain, lower pain thresholds still further. This facilitation of pain mechanisms by feeling responses can be thought of nowadays as a straightforward physiological mechanism (Russell, 1959), and from the practical aspect we may generally assume that those who most often complain of pain have an undue emotional reaction to their symptoms. The patient with intractable pain seems to have all levels of his nervous system facilitating his misery. The remarkable changes in central mechanisms are illustrated by the fact that stimulation of the sensory cortex in the appropriate area will reproduce intractable pains, say of the amputee, in the same way that they will reproduce focal epilepsy—another situation in which central thresholds have become grossly abnormal.

In intractable pain, however, all levels may contribute to the syndrome, and the handling of such a case becomes almost a battle between the C.N.S. of the patient and of his doctor.

Certainly the influence of feeling responses on thresholds is so important that the physician or surgeon is well advised to adopt a thoroughly confident attitude to the problem of relieving pain somehow or other, and I am convinced that special clinics are needed for these patients so that thresholds may be treated at all levels of the C.N.S. at the same time, and this of course includes what some will call the psychological level. These patients benefit greatly from the confidence provided by a well-conducted clinic. We have established a small once-weekly out-patient clinic of this kind and are able to handle about 100 new patients a year.

The study of peripheral thresholds is handicapped by large gaps in knowledge regarding the physicochemical processes concerned with the origin of a neuronal impulse which is interpreted as pain. For our present purpose it is not necessary to stray far into this difficult field, but it should be pointed out that we are still inclined to preserve some ideas about pain which require revision.

Thus there is still a widespread assumption that pressure on a nerve or nerve root provides an adequate explanation for the cause of many chronic pains. This is generally given as a cause of pain in disc protrusions causing sciatica or brachial neuropathy, but in fact, simple pressure on a peripheral nerve usually leads to a loss of conduction without causing any pain, so there is

often much doubt as to which are the tissues in relationship to which pain originates in these cases.

Direct stimulation of the neurons in a nerve leads to shooting pain to the periphery of the limb or other innervation concerned. In many cases of root neuropathy, however, other clinical features are more prominent. These include local tenderness of the nerve sheaths, sensitivity to stretch and increased tone in muscles supplied from that segment. Further, it is well known that symptoms are often relieved by maintaining a position in which the nerve trunks are kept relaxed or by injecting Xylocaine into a peripheral nerve trunk or into the hypertonic muscles near by. Both these observations indicate that in many instances the pain is a somewhat indirect consequence of the root "pressure", and is certainly not due simply to activation of the conducting fibres traversing the nerve (Russell, 1956).

My colleagues and I have been interested in chronic pain for many years, and we are increasingly impressed with the part played by the periphery in intractable pain. This is well illustrated by many cases of post-herpetic neuralgia, for here the pathology is in the posterior root ganglia and yet there are often areas of cutaneous hyperæsthesia.

However, as Noordenbos (1959) has recently emphasized, lesions at every level of the nervous system may occasionally cause hyperæsthesia; for example, this phenomenon may occur to a remarkable degree in the contralateral limbs after small wounds of the sensory cortex. The same is observed after partial division of the peripheral nerve, and it reaches a severe degree in cases of causalgia.

In all these instances a varying amount of sensory loss is associated with the hyperæsthesia as though the latter developed from a disturbance between the balance of various types of nerve fibres. Certainly Noordenbos has shown that the fibre spectrum in the nerves concerned with post-herpetic neuralgia, causalgia, and other partial nerve lesions shows a gross change with a relative increase in the thinner fibres.

Faulty regeneration may also be an important factor but this is only likely to be troublesome if there is denervated tissue into which surviving neurons can branch. It seems likely that widespread branching of surviving neurons may lead to nerve patterns which will form artificial synapses or even self-exciting systems, all of which must contribute to the afferent bombardment which emerges as pain.

There is a great variety of conditions causing chronic pain which are associated with hyperæsthesia at the periphery or in paraspinal tissues, and from the practical point of view it is specially important to realize that the neural activity in these cases must often originate in the hyperæsthetic zone. In other words, a damaged nerve may transform simple conducting impulses into a pattern which is interpreted as being painful. If this view is correct then the application of local anæsthesia at the periphery will abolish the pain temporarily. Our observations support this conception, for in conditions such as post-herpetic neuralgia, tender scars, coccydynia and phantom limb pain, peripheral local anæsthesia often has a dramatic temporary effect in giving relief.

This is a most important fact for there is increasing evidence that many chronic pains are most effectively relieved by attention to the periphery regardless of the site of the lesion. Such treatment may act in one of two ways:

It may raise thresholds at the periphery and so reduce the afferents reaching the C.N.S., or it may introduce a competing system of afferents which interfere physiologically with the noxious afferents. The scientific study of the second of these alternatives has received insufficient attention in the clinic, but is already being used by the physiologist to block conduction of one speed of fibre in order to study another speed.

On the other hand we have found that deliberate attempts to raise peripheral thresholds are most advantageous and successful in many chronic painful states. Thus in post-herpetic or the amputee's pain the following methods are often effective:

(1) Vigorous exercise to the painful area with repeated massage and firm bandaging of amputation stumps.

(2) Repeated procaine injections of hyperæsthetic areas.

(3) Frequent percussion of sensitive areas, with mallet and applicator, for tender neuromata (Fig. 1), or with electrical massager to sensitive skin (Fig. 2).

These last methods are conspicuously effective if properly and frequently applied. The vibration of an electric massager produces a traumatic block of nerve endings, and thus provides a safe method by which the patient can repeatedly provide himself with a local analgesic which develops into a traumatic destruction of sensitive nerves. Hyperæsthetic scars and tender neuromata can therefore nearly always be relieved by this method if it is properly applied.

Post-herpetic neuralgia has become more

amenable to treatment as we reported two years ago (Russell *et al.*, 1957), and we have come to look forward to dealing with these patients, especially if there is a lot of cutaneous hyperæsthesia.

The results with the amputee's pains are also often excellent (Russell and Spalding, 1950). The removal of the peripheral hyperæsthesia often leads to the pain being relieved to a remarkable extent. Thus treatment can often be directed successfully to an area which is far peripheral to the site of the main pathology.

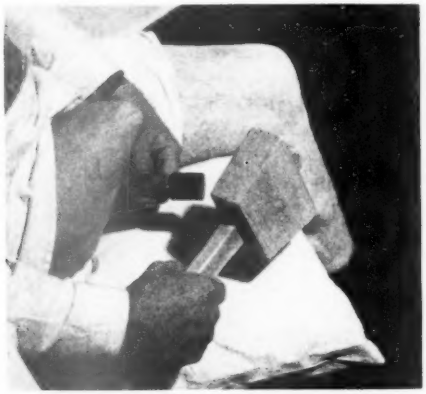

FIG. 1.—Percussion treatment of neuromata on sciatic nerve.

FIG. 2.—Mechanical massager being used to abolish hyperæsthesia in post-herpetic neuralgia.

However, we shall never get far in the study of chronic pain without considering the problem of central thresholds. In the first place it should be pointed out that modern views on physiology picture a continual bombardment of the C.N.S. by sensory impulses of all kinds. Thus the muscle spindles are probably never silent for long and it is possible that in cases of causalgia there is faulty regeneration of sensory fibres into peripheral muscular mechanisms which then discharge to the C.N.S. up pain pathways with every movement of joint or muscle.

We are all familiar with painful flexion spasms in cases of spastic paraplegia. We (Platt *et al.*, 1958) have recently found that the operation of transposing the hamstring tendon to the back of the femur has a remarkable effect in inhibiting these spasms and has proved to be an important advance in the treatment of this distressing condition. This principle of reversing the function of a muscle group seems to be an important one in this situation.

In relation to amputations I think that more attention should be given to there being as little denervated tissue as possible in the stump. Sprouting nerve fibres cannot branch far into tissue which is already fully innervated. Thus I am told that in old people amputations through the knee-joints has a very low incidence of tender stumps and phantom limbs (Cohen, 1959), and these must have very little denervated tissue.

Dr. Nathan's work has shown the complexity of the anatomical problem for he has studied cases of spinothalamic tractotomy in which a stimulus applied to the analgesic limb is felt at the segmental level of the surgical lesion. Clearly there must be a great deal of central spread from one level of the spinal cord to another, and we are all familiar with the patient whose pain spreads widely—far beyond the segments directly involved. These patients are often over-anxious and obsessed with their symptoms, but it is foolish just to label them as "functional", for their unfortunate emotional reaction provides perhaps the most powerful physiological stimulus there is for increasing the appreciation, that is to say a lowering of the thresholds, to peripheral sensations.

Thus the importance of the individual's general reaction to pain inevitably plays a part in every case. There is no sense in saying that one pain is functional and one organic, for unless the patient is inventing his story, all pains are both physiologically determined and functionally graded according to a wide variety of personal factors.

When it comes to treatment, however, there is little chance of changing the patient's long-established personal reactions—short of mutilating operations on the frontal lobe system. Confidence inspired by the pain clinic approach, however, will in itself do a lot from this point of view, and it is here also that drugs may be effective. It is to be hoped that when we understand more fully the nature of sensory synaptic transmission in the C.N.S. it may then become possible to interfere more directly with the central sensory thresholds. However, I should like to emphasize as strongly as possible that whatever the emotional or functional state of the patient suffering from chronic pain, in nearly all instances aggravating afferents are coming from the area to which the pain is referred and every effort should be made to interfere with this afferent bombardment, for if the peripheral state is corrected the central thresholds will often subside to a more normal level.

Thus the patient who is demoralized by a painful phantom limb will still get great benefit if the discharging neuromata are inactivated. The assessment of the part played by the periphery in provoking the pain can, and should, be assessed by systematically blocking the various parts and levels of the somatic and sympathetic nerves involved: this is an essential part of the investigation and may need a spinal anæsthetic for its completion. A study of the temporary effect of any such procedure is of the greatest importance in deciding future action. There is no doubt also that intrathecal injections, if used with skill, have an important part to play in intractable pain. I certainly have used intrathecal alcohol for thirty years (Russell, 1936) and am often surprised at the way in which the pain of malignant disease may be relieved for many weeks or months without there being any demonstrable loss of sensation.

Here it should be mentioned that Xylocaine injections given in an anatomical area concerned in some way with a chronic pain sometimes have an effect which far outlasts what would be expected, and it seems in some instances that the local block has an effect in breaking a vicious cycle. Thus local anæsthesia may have a curative as well as a diagnostic value, and of course it may be repeated two or three times a week for long periods should this be helpful. Thus we have found in cases of coccydynia that caudal anæsthesia gives relief which on a few repetitions may give many months of freedom from pain.

Another interesting approach to chronic pain (Fig. 3) is to aggravate central thresholds by injecting into the interspinous ligaments or paravertebral muscles (Whitty and Willison, 1958) an irritating solution of saline (0·5 ml. of 6%). Thus in the painful arm or scalp neuropathies associated with cervical spondylosis this may temporarily reproduce the arm or head pain complained of, and if Xylocaine is then added to the injection the pain disappears. This procedure is of great diagnostic value, and we use it to study cases of chronic head or face pain: it is also sometimes followed by prolonged relief of pain though the mode of action is then also somewhat mysterious. Injections which reproduce and remove a pain do, of course, have a great psychological effect, and this should be fully exploited by the medical and nursing staff for the patient's benefit.

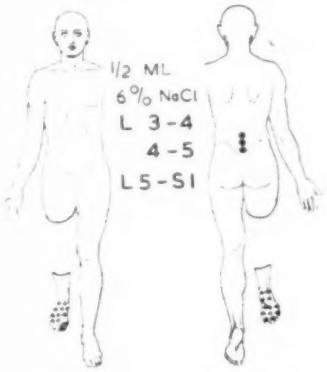

FIG. 3.—Study of phantom limb pains by injecting 6% saline into the interspinous ligament. Pains were reproduced in the phantom foot.

I am putting forward more problems than answers in this difficult field, but I should like to ask for further consideration of the possibility of introducing an afferent bombardment to the nervous system which will compete for attention with the local painful process. Maximal physical activity is perhaps a good example for this has a remarkable effect in raising pain thresholds. It is of course possible that many of the methods used in physiotherapy for relieving the pain of say arthritis are due to a mechanism of this type. Thus relief of pain by the application of heat is just as likely to act in this way as any of the other mechanisms put forward. The old methods of treating pains with electricity have become somewhat disreputable, but if we look on these as providing a physiological distraction they may assume a new mantle of respectability and importance. In this connexion I am often disconcerted by the reluctance of physiotherapists

to treat cases of malignant disease. They apparently fear that the method they use may hasten the growth of the tumour. I would doubt, however, whether there is any foundation for such a view, and would encourage them to provide as much counter-irritation or other form of physiological diversion as they can.

To summarize, I would suggest that the successful therapist for intractable pain treats the problem like a game in which he endeavours to outmanœuvre the tricks performed by the C.N.S. of his patient. He has many different moves he can play. Some depend on simple procedures which checkmate the mechanisms, but others are assisted by the deception of the poker player and the confidence of the quack.

I might add that my colleagues, to whom I am greatly indebted for assistance, think that I am too optimistic about the results of treatment, but I think it is important to be over-confident in treating pain, so I make no apology.

REFERENCES

COHEN, S. M. (1959) Personal communication.
NOORDENBOS, W. (1959) Pain. Amsterdam.
PLATT, G., RUSSELL, W. R., and WILLISON, R. G. (1958) *Lancet*, i, 757.
RUSSELL, W. R. (1936) *Lancet*, i, 595.
—— (1956) *Proc. R. Soc. Med.*, **49**, 198.
—— (1959) Brain: Memory: Learning. Oxford.
——, ESPIR, M. L. E., and MORGANSTERN, F. S. (1957) *Lancet*, i, 242.
——, and SPALDING, J. M. K. (1950) *Brit. med. J.*, ii, 68.
WHITTY, C. W. M., and WILLISON, R. G. (1958) *Lancet*, ii, 226.

Professor Norman M. Dott (Edinburgh):

There are some attributes and characteristics of pain that are practically useful in planning treatments.

Its *intensity* is obviously important. Its *duration* is equally so. We all know we can easily bear a severe pain if its duration is less than one second. A much less intense pain lasting for days becomes intolerable. A relatively slight pain lasting for months or years wears us out—and becomes unbearable. The expected duration of pain must greatly influence our management of it.

Conscious pain can be inhibited by preoccupation, by other temporarily dominant emotions and by hypnosis. It can be augmented by certain allied emotional states—depression or anxiety. The *psychological* management of pain is of great importance and should receive the physician's careful attention.

Analgesic drugs can abolish or lessen pain. Those with few undesirable side-effects can cope only with pain of moderate severity. The more potent analgesics all have serious objectionable effects, and must be used with discretion—especially with regard to the duration of their use. This is often related to our estimate of the patient's life expectancy.

Our patients' *pain tolerance* varies greatly. I do not believe that a neurotic patient's overvaluation of pain is a contraindication to surgical treatment. Rather it is an indication in favour of it, for ultimately it is the *patient's valuation* of his pain that is of real importance. I may add that in my experience both simulated and exclusively psychogenic pain are very rarely encountered. Practically all the patients I have seen who complain of pain have some physical basis for it. The pain may be slight and greatly over-estimated—but it is there; and either the over-estimation or the pain or both require purposive treatment.

Pain has a dual significance: (1) a localized, physical sensation of a particular and recognizable quality, (2) an experience that is emotionally distressful. The latter is much the more important from the patient's point of view.

Pain is variously induced by appropriate stimulation of the sensory end-organs of the skin, deeper tissues, viscera (including blood vessels)—physiological; or by pathological lesions on the afferent conduction system from the body—at any site on the pathway from peripheral nerves to thalamic level. So induced the stimuli reach "consciousness". Consciousness—that state of awareness—is believed to be sustained basically at the diencephalon, and as regards its emotional aspects in the archipallium around it, and as regards more detailed discrimination in the more distant neopallium. Consciousness of pain is probably similarly disposed. Thanks to these arrangements it is possible—by means of *leucotomy*—to decrease the emotional or affective appreciation of pain as contrasted with its physical perception. Unfortunately the operation alters the affective state of the patient on a wider front than pain distress alone, rendering the person more superficial emotionally, a state characterized by apathy, poverty of judgment and lack of initiative. Its use is therefore limited to patients in whom these disadvantages can be reasonably accepted in exchange for mitigation of pain, for example, distressful cancer cases or aged obsessionals. The technical procedure will probably be improved upon by more limited and strategically placed fibre interruptions by stereotaxic techniques; but at present only an inter-

ruption extensive enough to produce the disadvantages mentioned is effective for pain distress.

Let us approach the problem from the periphery. We wish to prevent the intractable pain impulses from reaching consciousness. We may interrupt the pathways up which the impulses travel.

We shall usually avoid section of *peripheral nerves* for three reasons: (1) Nerve fibres regenerate at this level so that the effect is temporary. (2) Most nerves carry both motor and sensory fibres and the sacrifice of the former is undesirable. (3) Unpleasant dysæsthesiæ result during the later stages of regeneration, which may be more disagreeable than the original pain.

We may interrupt the afferent pathways alone at *posterior root* level—posterior rhizotomy. At this level motor fibres are not involved and regeneration does not take place. However, all afferent impulses from the territory of that root are blocked. This may be disadvantageous in the limb supplies from loss of proprioception and touch, rendering the limb useless; and from increased liability to ulceration from loss of the local neural inflammatory reflex—the trophic effect. Further sensory integration in the spinal cord is so affected by such total loss of afferent impulses that an unpleasant impression is conveyed to consciousness—varying from a positive sense of numbness to various superimposed paræsthesiæ of swelling—of tension—sometimes actually described as pain. In general, therefore, posterior rhizotomies are to be avoided; though, for anatomical reasons, we are obliged to employ this procedure in dealing with the sensory cranial nerves and the upper four cervical nerves.

Before leaving rhizotomy, however, I should mention the therapeutic value of Maher's localized *intrathecal injection* of anhydrous *phenol* in Myodil. This can be accurately localized to affect the desired posterior roots and is especially valuable in treating pain due to implication of spinal nerves by malignant disease. It acts by effecting a quantitative reduction of the conducting fibres in the affected posterior root. This reduction of afferents does not produce a loss of sensibility appreciable to clinical tests, yet it does abolish spontaneous pain of moderate severity. It is insufficient to abolish very severe pain—especially when many roots are involved in its conduction. There is usually some recovery of fibres after three to six months. It can be repeated effectively. The measure has none of the disadvantages of complete surgical rhizotomy. The effect appears to be a quantitative one on all types of fibres and supports the idea that pain conduction at this level is a quantitative rather than a separate, specific function.

Vastly superior in effect and in avoidance of unpleasant side-effects is the operation of *cordotomy*—anterolateral tractotomy. This permanently severs the specific pain and temperature impulse conducting tract at a level above spinal sensory integration and dissociation into specific functional tracts. There is no sense of unpleasant numbness. At most there is a mild paræsthesia of pleasant warmth. Otherwise the patient is unaware of any abnormality of sensation, except under test conditions when he appreciates that he cannot feel pain or temperature in the affected zone. The usefulness of arm or leg is unimpaired and there is no "trophic" liability. This, then, is the operation of choice for most intractable pains arising in the body from C.5 downwards. Sensory integration and dissociation into sufficiently defined tracts occupies at least five segments in the thoracic region and the section must therefore be at least so far above the desired analgesic level. Those functions are more compressed in the cervical cord and the tract section must be at least three segments above the desired level. It may be noted that analgesia is never absolute—a strong painful electric stimulus will still cause pain in the analgesic area. It is not enough, for practical purposes, to produce a hypalgesia for pin-prick only. Severe intractable pains produce a stimulus much stronger than that. I am accustomed to test the desired degree of hypalgesia with a barbarous pincer applied to a fold of skin. When pain from that stimulus is abolished, this usually suffices for the abolition of the severest pains of intractable disease. It will be noted that this implies that the tract section is made with the patient conscious and able to co-operate.

With these precautions consistently satisfactory results can be achieved, and complications, such as interference with bladder control, can be avoided. Over the first few months after cordotomy there is a tendency for the level of analgesia to fall by two or three segments; and it is safer to make the level at the time of operation at least four or five segments higher than the source of pain. There is a tendency for the degree of hypalgesia to lessen over the years following cordotomy. If the initial degree was deep enough this rarely implies such recovery that spontaneous pain breaks through again. I have seen it do so, however, in a limited field, and have countered it by superadding a limited posterior rhizotomy.

At C.1 and upwards the anatomy is complicated by the descending cranial sensory

(trigeminal, intermedius, glossopharyngeal and vagus) input and its pain-conducting decussation diffusely within the brain-stem. Also about mid-medullary level the pain tract begins to pass fibres to the central reticular formation and does so progressively up to mid-brain level. At upper mid-brain level the specific spinothalamic tract has lost more than half its fibres. When one divides it here superficial pin-prick is lost over the contralateral body including the face; but deep, slow pain, presumably travelling via the central reticular formation to consciousness, is not abolished. Further, the interference—perhaps imbalance—of sensory integration so engendered, results in positive and constant discomfort.

So we have leucotomy with its disadvantages above, and we have cordotomy with its advantages below—but only valid for analgesia up to C.4. Many of the pains arising above C.4 level can be dealt with by posterior rhizotomy with its disadvantages—including trigeminal and glossopharyngeal neuralgia and facial migrainous neuralgia and pain from malignant disease.

This leaves out of account those states that depend on painful stimuli arising centrally in the pain-conducting pathways within the brain-stem and up to thalamic level, and that are independent of afferent stimuli from the periphery. These pains of central origin have so far defied surgery, and can be only inadequately palliated by analgesics and philosophy. They are quite common, and of life-long duration. They cry out for effective treatment. One would suppose that they require interruption of the pain pathways about thalamic level or just above it. Available evidence suggests that at this level the slow, diffuse, dull pain that will become emotionally charged and intensely distressing as it reaches consciousness is already anatomically separated from the fast, localized, sharp pain pathway. The former, which we should most desire to destroy, may also be too diffuse for convenient anatomical destruction. As you know, thalamotomies are being effected by stereotaxic techniques and we may succeed in these aims; but I cannot say we have done so yet. It may well require more than one lesion at or near thalamic level to secure a cordotomy-like effect for these upper reaches of the neuraxis. We shall continue to search for this goal.

Time forbids that I should do more than mention the interruption of cardiac and other visceral sympathetic nerves for pain of visceral origin. Nor need I dwell on sympathectomy for causalgia and sympathetic dystrophies for here we are really treating a cause of pain—breaking a vicious circle of local reflexes that maintain the painful state.

Dr. P. W. Nathan (London):

Unilateral Cordotomy

I propose to restrict my remarks to unilateral cordotomy. The reason for this is that in my opinion unilateral cordotomy is a good operation, whereas bilateral cordotomy, when performed for pelvic or lower abdominal pain, is an operation having certain inevitable complications; if it renders all pelvic structures analgesic it will destroy control of the bladder and the bowel. This may be the price that the patient has to pay to be relieved of pain. Unilateral cordotomy is an operation which may have no complications at all; and therefore it is a very good operation. This being so, I hope you will forgive me if I run through some elementary facts which are useful in guiding one when to carry out a unilateral rather than a bilateral cordotomy. All these remarks apply only to the intractable pain of cancer.

Indications for unilateral cordotomy.—In considering the unilateral operation, we have to think how far and how fast the growth is spreading, what is the general condition of the patient and whether he will die before the growth spreads to the other side.

When the growth is in the pelvis useful information may be obtained from a descending pyelogram; for not only does it tell us something of renal function, but it may also tell us if one or both ureters are blocked. The neurological signs are useful; ascertaining if the peripheral nerves, the nerve trunks or the roots are involved provides information about the location of the growth.

Above the pelvis, pelvic carcinomata commonly spread to involve the aortic and the para-aortic glands. Here the psoas muscle and the first, second, third and fourth lumbar nerves running within it may be involved. When these are the tissues involved by the growth, it may be reasonable to do a unilateral cordotomy. Involvement of the back muscles, a painful condition, may be satisfactorily dealt with by the unilateral operation. If the growth involves an abdominal viscus, such as the pancreas, stomach or duodenum, I think one has to do a bilateral cordotomy. If it involves a mid-line structure which is still present, such as the rectum or prostate, the operation has to be bilateral. But by the time the neurosurgeon sees the patient, the organ in which the growth originated has usually been removed; in this case, the operation does not need to be bilateral. The growth may spread entirely unilaterally with the

pain remaining unilateral; in such a case it may be satisfactory to do a unilateral cordotomy.

When the growth involves the vertebræ, it does not necessarily mean that the operation has to be bilateral. If it involves the bodies, I think it does have to be bilateral; that is, it has to be bilateral if one is going to do a cordotomy at all. For by the time the body is involved, collapse will soon follow; and unless one strives to keep the patient alive he will soon die after this has occurred. If the pedicles or the transverse processes of the vertebræ are involved it is difficult to decide whether the operation should be unilateral or bilateral; it may be possible to do the unilateral operation, the patient dying before the growth spreads to the other side. When the secondaries involve the heads of the ribs and the region of articulation of the ribs with the vertebræ, a common place for secondaries, a unilateral cordotomy may be satisfactory. If the growth involves the ribs further laterally, obviously a unilateral operation suffices.

In addition to these considerations there are one or two special cases. I am sometimes asked if it is all right to do a cordotomy in the presence of a colostomy; actually neither the unilateral nor the bilateral operation affects a colostomy. When a patient has had the ureters transplanted, which is commonly done nowadays, I think that any cordotomy is contraindicated; for the patient will not have enough control of the anal sphincter to remain continent with a rectum containing liquid fæces. When there is a unilateral carcinoma of the bronchus and/or a Pancoast type of tumour, there are certain consequences affecting the results of a unilateral cordotomy. The tumour reduces the amount of functioning lung tissue on the side on which it is situated; if it is a Pancoast tumour, it may also involve the phrenic nerve, and the recurrent laryngeal nerve. The unilateral cordotomy, being done on the opposite side and well cranial to the phrenic nucleus, stops respiration, both diaphragmatic and intercostal, for twenty-four hours or more and diminishes it for about ten days. And so, during this time, the patient will have only the amount of functioning lung that he has left not involved by the tumour; if there is a phrenic nerve palsy, there will be even more embarrassment to respiration. If there is also a recurrent laryngeal nerve palsy, the patient cannot cough. With such disabilities, these patients may die. I do not necessarily think that a unilateral cordotomy is ruled out, but one must go into this situation with one's eyes open, knowing what may happen, and being prepared to have the patient treated by artificial respiration after the operation.

Complications of unilateral cordotomy.—Walking: this may not be affected at all; at worst, the ipsilateral limb may be rendered very weak. Micturition: the patient may experience no disorder whatsoever; at worst, there can be inability to start micturating; but this does not last for more than two or three weeks. Defæcation: there may be no disorder at all; at worst there can be very severe constipation, and if the patient gets diarrhœa, he may have great difficulty in remaining continent. Paræsthesiæ: paræsthesiæ in the part of the body rendered analgesic are fortunately rare. They are very unpleasant, but all patients deny that they are painful. From giving spinal anæsthetics in these cases I have found that they do not arise at the cordotomy incision; they are blocked by blocking all the peripheral nerves from the part of the body where they are felt.

The commonest complication is that the patient feels the pain immediately after the operation on the opposite side of the body. This is associated with a reference of sensation that can be demonstrated. It is a common complication; I have found it in 15 out of 35 cases of unilateral cordotomy. It can occur with division of the spinothalamic tract at any level, also with division of the tract by a thrombosis of the posterior inferior cerebellar artery in the medulla oblongata. This reference of sensation is not restricted to unilateral cordotomies, though it is commoner in them. In a bilateral cordotomy, the pain may be referred to the region between the zone of analgesia and the normally innervated part. This constitutes one of the causes of pain continuing in this region for months after the cordotomy.

After unilateral cordotomy, painful stimuli applied within the analgesic zone may be felt in an analogous part of the body on the opposite side; this is illustrated in Fig. 1. In Fig. 2 is illustrated a common state. After the unilateral cordotomy, the stimuli applied within the analgesic area are felt on the opposite normally innervated side but in a region opposite to that where the pain was present before the operation. The possible mechanism of this reference of sensation I have discussed elsewhere (Nathan, 1956). The pain felt on the opposite side to the original pain tends to be similar in character, but it may not be exactly the same; it tends to have the character of deep pain, of an aching type. It is always less severe than the original pain, but it may be severe enough to need a second cordotomy. Whether the stimulus applied to the analgesic side is one of pain, hot or cold, of distension of the bladder or rectum, the sensation felt on the normally innervated side is

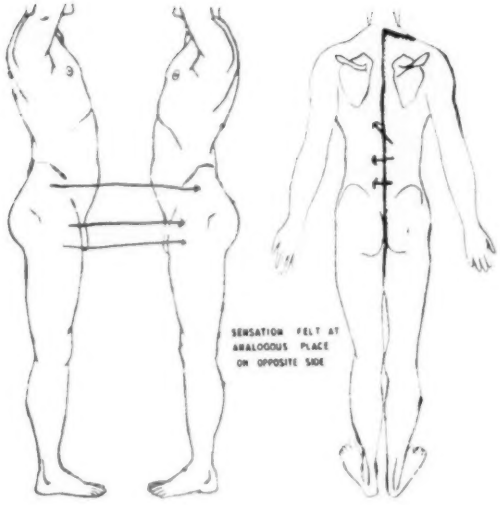

FIG. 1.—Stimuli applied within the analgesic zone are felt at the analogous position, or near the analogous position, in the normally innervated part of the body. The shaded line shows the limit of the analgesic zone.

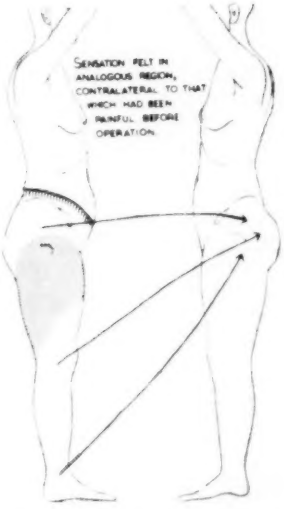

FIG. 2.—Stimuli applied within the analgesic zone are felt at a place on the normally innervated side of the body corresponding to that which had been painful and tender before the unilateral cordotomy. The shaded line shows the limit of the analgesic zone and the stippled area is that where the pain and tenderness had been experienced before the operation.

one of pain. In some cases all the sensations are referred to one constant area. Such an area may have been tender before the cordotomy or it may not have been in any way abnormal. We have found in most cases no cause for this choice of area to which sensation is referred; nothing abnormal was found *post mortem* and no histological abnormalities have been found in that segment of the cord. The fact that a second cordotomy removes the pain and the reference of sensation seems to indicate that this mechanism is a spinal one, and not thalamic.

When I originally wrote about this, I wrote that only those stimuli that set up impulses in the spinothalamic tract cause this reference of sensation in cases with division of the spinothalamic tract. Since that time, I have seen one patient in whom this was not so; this patient himself found that the sensation of stroking or pressing on his analgesic thigh was felt on the opposite thigh; in his case all stimuli applied to the analgesic region evoked referred sensations.

I now think that in all cases of unilateral cordotomy when the pain is felt on the opposite side within fourteen days of the operation, this is due to this mechanism of reference of sensation. I do not believe that this pain was present before the cordotomy and not noticed by the patient.

Summary

I have tried to give the impression that in many cases of cancer it is better to do a unilateral than a bilateral cordotomy, for the unilateral operation may have no complications whatsoever. When there are complications, they may consist of weakness of the ipsilateral lower limb, an inability to start micturition lasting about fourteen days, severe constipation, rarely paræsthesiæ, and commonly a condition in which some pain is felt after the operation on the opposite side.

REFERENCE

NATHAN, P. W. (1956) *J. Neurol. Psychiat.*, **19**, 88.

BOOKS RECEIVED FOR REVIEW

Congress: Gastroenterology. Proceedings of the World Congress of Gastroenterology and the 59th Annual Meeting of the American Gastroenterological Association, May 25–31, 1958. In 2 volumes. pp. xxxv + 1363. London: Baillière. 160s. 1959.

Cruickshank (R.), and **Glynn (A. A.),** eds. Rheumatic fever. The Proceedings of a Seminar held at the International Children's Centre, Paris, 25–27 September, 1956. pp. 193. Oxford: Blackwell. 25s. 1959.

Flatt (A. E.). The care of minor hand injuries. pp. 266. St. Louis: Mosby. London: Kimpton. 71s. 6d. 1959.

Garland (G. W.), and **Perkes (R. C.).** Midwifery (A textbook for pupil midwives). pp. xi + 290. London: English Universities Press. 21s. 1959.

Havener (W. H.). Synopsis of ophthalmology. pp. 288. St. Louis: Mosby. London: Kimpton. 50s. 1959.

International review of neurobiology. Vol. 1. pp. xii + 383. New York: Academic Press. $10. 1959.

Jacobs (A. L.). Arterial embolism in the limbs. pp. xii + 200. Edinburgh and London: Livingstone. 35s. 1959.

Lindahl (J.). Somatic complications following legal abortion. Translated by S. H. Vernon. pp. 182. Stockholm: Scandinavian University Press. London: Heinemann. 42s. 1959.

Lucas (R. B.), and **Kramer (I. R. H.).** Bacteriology for students of dental surgery. 2nd ed. pp. viii + 288. London: Churchill. 27s. 6d. 1959.

Moser (R. H.). Diseases of medical progress. pp. xvi + 131. Springfield, Ill: Thomas. Oxford: Blackwell. 36s. 1959.

Murphy (D. P.), and **Abbey (H.).** Cancer in families. A study of the relatives of 200 breast cancer probands. pp. x + 76. Cambridge, Mass.: Harvard University Press. London: Oxford. 20s. 1959.

Peer (L. A.), ed. Transplantation of tissues. Vol. 2. pp. xiii + 690. London: Baillière. 160s. 1959.

Roaf (R.), Kirkaldy-Willis (W. H.), and **Cathro (A. J. M.).** Surgical treatment of bone and joint tuberculosis. pp. viii + 137. Edinburgh and London: Livingstone. 30s. 1959.

Rodger (F. C.). Blindness in West Africa. pp. xiv + 262. London: Lewis. £3 10s. 1959.

Ryan (R. E.), Thornell (W. C.), and **von Leden (H.).** Synopsis of ear, nose and throat diseases. pp. 383. St. Louis: Mosby. London: Kimpton. 50s. 1959.

Voisin (A.). Soil, grass and cancer. Translated by Catherine T. M. Herriot and Dr. Henry Kennedy. pp. xvii + 302. London: Crosby Lockwood. 30s. 1959.

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Congress: Gastroenterology. Proceedings of the World Congress of Gastroenterology and the 59th Annual Meeting of the American Gastroenterological Association, May 25–31, 1958. In 2 volumes. pp. xxxv + 1363. London: Baillière. 160s. 1959.

Cruickshank (R.), and **Glynn (A. A.),** eds. Rheumatic fever. The Proceedings of a Seminar held at the International Children's Centre, Paris, 25–27 September, 1956. pp. 193. Oxford: Blackwell. 25s. 1959.

Flatt (A. E.). The care of minor hand injuries. pp. 266. St. Louis: Mosby. London: Kimpton. 71s. 6d. 1959.

Garland (G. W.), and **Perkes (R. C.).** Midwifery (A textbook for pupil midwives). pp. xi + 290. London: English Universities Press. 21s. 1959.

Havener (W. H.). Synopsis of ophthalmology. pp. 288. St. Louis: Mosby. London: Kimpton. 50s. 1959.

International review of neurobiology. Vol. 1. pp. xii + 383. New York: Academic Press. $10. 1959.

Jacobs (A. L.). Arterial embolism in the limbs. pp. xii + 200. Edinburgh and London: Livingstone. 35s. 1959.

Lindahl (J.). Somatic complications following legal abortion. Translated by S. H. Vernon. pp. 182. Stockholm: Scandinavian University Press. London: Heinemann. 42s. 1959.

Lucas (R. B.), and **Kramer (I. R. H.).** Bacteriology for students of dental surgery. 2nd ed. pp. viii + 288. London: Churchill. 27s. 6d. 1959.

Moser (R. H.). Diseases of medical progress. pp. xvi + 131. Springfield, Ill: Thomas. Oxford: Blackwell. 36s. 1959.

Murphy (D. P.), and **Abbey (H.).** Cancer in families. A study of the relatives of 200 breast cancer probands. pp. x + 76. Cambridge, Mass.: Harvard University Press. London: Oxford. 20s. 1959.

Peer (L. A.), ed. Transplantation of tissues. Vol. 2. pp. xiii + 690. London: Baillière. 160s. 1959.

Roaf (R.), Kirkaldy-Willis (W. H.), and **Cathro (A. J. M.).** Surgical treatment of bone and joint tuberculosis. pp. viii + 137. Edinburgh and London: Livingstone. 30s. 1959.

Rodger (F. C.). Blindness in West Africa. pp. xiv + 262. London: Lewis. £3 10s. 1959.

Ryan (R. E.), Thornell (W. C.), and **von Leden (H.).** Synopsis of ear, nose and throat diseases. pp. 383. St. Louis: Mosby. London: Kimpton. 50s. 1959.

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President—ALEC W. BADENOCH, M.A., M.D., Ch.M., F.R.C.S.

Meeting
March 19, 1959

THE following specimens were shown:

Fibromyxosarcoma of Kidney.—Mr. R. J. RYALL (for Sir ERIC RICHES).

Dysplastic Kidney with Stone Formation.—Mr. HOWARD G. HANLEY and Dr. R. C. B. PUGH.

Retroperitoneal Liposarcoma Involving Kidney and Suprarenal.—Mr. M. F. NICHOLLS.

Co-existing Parenchymal Hypernephroma and Papillary Carcinoma of Renal Pelvis.—Mr. ALEX E. ROCHE.

Renal Carcinoma with Metastasis to Bladder.—Mr. RICHARD E. SHAW.

(1) **Tumour of the Ureter Extending to the Ureteric Orifice.** (2) **Cancer of the Kidney Presenting as a Varicocele.**—Mr. J. H. CARVER.

Giant Ureteric Calculus.—Mr. PAUL SAVAGE.

Recurrent Leiomyosarcoma of Bladder.—Mr. W. B. WATERFALL.

Actinomycosis of Kidney.—Mr. HOWARD G HANLEY.

Meeting
April 23, 1959

DISCUSSION ON PARATHYROID DISEASE [*Abridged*]

Professor C. E. Dent (London):

Medical Aspects of Primary Hyperparathyroidism

Clinical.—There are two different diseases which happen to be called by the same name, primary hyperparathyroidism: (*a*) "without bone disease", presenting as a complication of hypercalcæmia or hypercalciuria, or with no symptoms at all (but still a bad prognosis), (*b*) "with bone disease", presenting in the same way as (*a*), but more often with symptoms related to the skeleton and always with some radiological changes recognizable as being due to hyperparathyroidism. These latter may be generalized or localized, or both.

Cases without bone disease are much more common than are those with bone disease and are much more difficult to diagnose as they may be indistinguishable clinically from many other diseases, especially those with renal stone formation.

Biochemical.—This is the only way to diagnose cases without bone disease. It is a great help in cases with bone disease. Except for the plasma phosphatase (*see below*) the biochemical criteria are the same for both diseases.

Plasma (or serum) total calcium should be more than 10·5 mg./100 ml. if properly done. This is the key diagnostic measure; a raised calcium is always pathological but the differential diagnosis of hypercalcæmia should be borne in mind (osteolytic bone tumours; vitamin-D overdose; sensitivity to vitamin D, as in sarcoidosis; sudden immobilization, especially in Paget's disease, &c.). The hypercalcæmia should not fall on giving cortisone (150 mg. a day for ten days). There are many ways of doing the calcium wrongly. We fail to confirm hypercalcæmia in over half of the patients referred to us from elsewhere on account of this finding. Laboratory mistakes are very easy to make. Less well known are (*a*) the effect of venous occlusion in raising the total calcium (Philpot, 1958); (*b*) the diurnal variations (usually rises after meals); and (*c*) the effect of a high phosphate diet in lowering the total calcium and *vice versa* (Philpot, 1958). A raised ionized calcium (greater than 6·2 mg./100 ml.), when it can be done, is much more significant than a raised total calcium. Rarely, in primary hyperparathyroidism, the ionized is raised when the total is normal.

Plasma inorganic phosphate (expressed as phosphorus) should be less than 3·0 mg./100 ml. unless there is renal damage, when it may be normal or raised. Phosphate clearances (reviewed by Nordin, 1958) are usually raised, but this finding is non-specific and occurs in many other diseases. A normal phosphate clearance, however, makes primary hyperparathyroidism very unlikely.

Plasma alkaline phosphatase must be normal if the bone X-rays are normal and raised if they show hyperparathyroid changes.

We no longer perform the urine calcium determination on a low calcium diet, which was recommended by Albright and Reifenstein (1948) as a diagnostic aid. The urine calcium is usually

raised in primary hyperparathyroidism but this is unhelpful in diagnosis as it is so often raised in the other diseases which come into the differential diagnosis. A slight degree of renal damage should lead one to expect it to be normal or even low.

Radiological.—Of little help in cases without bone disease. Kidney X-rays are non-specific. Stones, if present, may be single, multiple, unilateral or bilateral, they must be fairly radio-opaque and must not look like cystine stones. Nephrocalcinosis, if present, strengthens the evidence in favour of hyperparathyroidism. In cases with bone disease the X-ray appearances may be pathognomonic of hyperparathyroidism but this does not indicate in itself whether it is primary or secondary. Sometimes the radiological changes are very generalized, comprising widespread fuzziness of the trabeculations and subperiosteal erosions in various characteristic sites. We think this is pathognomonic and probably occurs with relatively acute severe hyperparathyroidism. In certain cases subperiosteal erosions are not symmetrically distributed or may even be absent, and the bone lesions may present as localized "cystic" spaces or expansions of the bone. Such cases may cause more difficulty in radiological diagnosis. We think this latter probably indicates a longer lasting, less severe form of the disease. In searching the skeleton for likely changes due to metabolic bone diseases, Dr. C. J. Hodson and ourselves have standardised a set series of useful bone X-rays which we call for convenience the "abbreviated skeleton". This comprises lateral skull, chest P.–A., lateral lumbar vertebræ, renal areas, pelvis, both knees, both hands and wrists. Generalized rarefaction ("decalcification") of the skeleton is not usually present with the other bone changes of hyperparathyroidism and if present is non-specific and does not help in diagnosis. In this we disagree with the opinion in this matter expressed by Albright and Reifenstein (1948), and more recently by Nordin (1958).

Pathological.—The various forms of tumour, whether adenoma or primary hyperplasia, are not related in any way to the clinical, biochemical or radiological findings. There is no way of anticipating what will be found at operation. We have had a patient who had four normal parathyroid glands in the neck and a chief cell adenoma in the mediastinum (Rose, 1959). The surgeon can, therefore, confirm the diagnosis, but can never for certain exclude it.

Secondary Hyperparathyroidism

This occurs rarely in steatorrhœa, and may produce radiological bone appearances indistinguishable from those in primary hyperparathyroidism with bone disease. The other medical and clinical findings are usually sufficiently obvious to prevent confusion with primary hyperparathyroidism. The total and ionized plasma calcium are never raised in cases secondary to steatorrhœa.

It very frequently occurs as a complication of chronic renal failure. Such patients occasionally present with symptoms of bone disease and can be readily confused with cases of primary hyperparathyroidism with bone disease since the bone X-rays are identical. The distinction is not always easy and is an important one to make as the treatment of secondary hyperparathyroidism is medical and of primary is surgical, the treatment in both cases being very good. Moreover, primary hyperparathyroidism is often associated with chronic renal failure.

In hyperparathyroidism secondary to renal damage: (*a*) Plasma ionized calcium level is normal or low; total calcium is usually (not always) normal or low. (*b*) The ionized and total calcium levels cannot be raised above normal by giving aluminium hydroxide by mouth. (*c*) A therapeutic trial of medical treatment (Dent *et al.*, 1959) will cure the bone disease.

It may rarely occur also with other causes of rickets or osteomalacia.

Review of our First 40 *Successfully Operated Patients at University College Hospital*, 1949–1958

In this time 42 patients were operated upon, two mistakes having been made, as will be indicated below by Mr. D. R. Davies. No other neck explorations were undertaken for the discovery of parathyroid tumours.

Of these 40 patients, 12 were male, 28 female. 8 were of the form with bone disease, 27 without bone disease. These latter 35 presented with symptoms or signs as mentioned above. In some of them the presenting sign was discovered accidentally, as for instance when a renal stone was discovered on X-rays done for other purposes. The remaining 5 patients, however, were unusual in that the right blood tests to make the diagnosis were performed for entirely the wrong reasons, for instance, misinterpretation of X-rays, or unusual enthusiasm for biochemical investigation. The age at operation was mainly in the period around 45–55, but as symptoms sometimes had been present for a long time, in one case over thirty years, the age when symptoms were first noted covers a much wider age group, and indeed was fairly evenly distributed over the whole range of late adolescent and adult life. Interesting clinical features noted were that about a third showed corneal calcification ("band keratitis") and about an equal number showed marked improvement in mental well-being after the operation. Our cases with and without bone

disease, as diagnosed radiologically, separated well into two groups on the basis also of their alkaline phosphatase levels, those without bone disease all being below 15 King-Armstrong units and those with bone disease being always above 18 King-Armstrong units, usually well above this. 5 of 32 patients without renal damage showed normal urine calcium outputs on normal diets. 6 out of 8 with renal damage had normal or low urine calcium. An interesting feature was that there was much more severe renal damage in the cases with bone disease than in those without bone disease and when it occurred the renal damage could not be explained on the basis of complications due to stone formation, nor was it due to a more severe hypercalcæmia, nor to a longer known duration of the disease.

We conclude that our diagnostic criteria are now moderately good for making the diagnosis reliably. It is a rewarding diagnosis to make as the patients, usually quite ill, generally make a very good recovery after operation. The disease is probably much more common than it is usually considered to be. One finds many more cases when one looks hard for them; most cases have been undiagnosed with symptoms for some years and our several completely accidental diagnoses could hardly have occurred if the disease were really rare. We therefore strongly recommend that simple biochemical (plasma calcium and phosphorus) determinations should be done on flimsy grounds when practical, but only, of course, when the technique is above question. We are very interested in the sharp distinction found by us between the with and without bone disease forms. We do not know the explanation for this but our data are against the only serious theory so far advanced—Albright and Reifenstein (1948)—that it depends on the previous dietary intake of calcium. These and other authors have never claimed a sharp distinction between the two diseases. We wonder if it means that two different hormones are secreted by the parathyroid gland.

REFERENCES

ALBRIGHT, F., and REIFENSTEIN, E. C. (1948) The Parathyroid Glands and Metabolic Bone Disease. London.

DENT, C. E., HARPER, C. M., and PHILPOT, G. R. (1959). In preparation.

NORDIN, B. E. C. (1958) *Advanc. internal Med.*, **9**, 81.

PHILPOT, G. R. (1958) Calcium Metabolism in Humans. Ph.D.(Lond.). Thesis.

ROSE, G. A. (1959) *Proc. R. Soc. Med.* To be published.

Mr. D. R. Davies (London):

Primary hyperparathyroidism may be suspected on clinical or X-ray findings but a diagnosis acceptable as an indication for surgical exploration can only be made by biochemical investigation. Expertly performed and critically reviewed, the investigations will exclude other causes of hypercalciuria and hypercalcæmia and establish a diagnosis of primary hyperparathyroidism. Between 1949 and 1958 at University College Hospital a confident diagnosis of primary hyperparathyroidism was made in 42 cases. The third case proved to be a sarcoidosis and in one no tumour or hyperplasia was found despite 3 explorations, 1 elsewhere and 2 at University College Hospital, and the patient remained hyperparathyroid. Sarcoidosis can now be excluded by biochemical investigation.

The role of surgery is quite definite. Primary hyperparathyroidism may result from primary hyperplasia, adenoma or carcinoma. There is no way of distinguishing between these three pathologies except by operation and no way of treating them except by extirpation. Operation is therefore indicated by a diagnosis of primary hyperparathyroidism, first to establish the type of change in the parathyroid glands, then to carry out the appropriate extirpation.

Primary hyperplasia involves all the parathyroid tissue present. In 30 cases of primary hyperparathyroidism due to adenomas 3 had adenomas in 2 glands. The exploration is therefore not a search for an enlarged parathyroid but a search for all the parathyroid glands in the neck and mediastinum. The usual practice is a complete exploration of the anterior compartment of the neck from the hyoid to the manubrium as the first stage, and, when indicated, exploration of the mediastinum at a later date.

At the first operation the parathyroids found are proved by frozen section and their positions carefully mapped. If an adenoma is found that gland is removed. If the change is primary hyperplasia the parathyroid tissue is reduced to a mass equivalent to a sphere 1 cm. in diameter.

A second exploration of the neck is indicated: (1) If no parathyroids were found. (2) If one parathyroid was found. (3) If two parathyroids were found on the same side of the neck. (4) If two parathyroids were found on opposite sides of the neck but at very different levels. (5) If operation was followed by temporary correction of serum calcium levels.

The mediastinum is explored: (1) If, after a full and careful dissection of the neck, two parathyroids were found one on either side and they were above the inferior thyroid artery. (2) If four normal parathyroids were found in the neck. (3) If four parathyroids showing primary hyperplasia were found in the neck and reduced to a mass 1 cm. in diameter but the hyperparathyroidism continues.

Meeting
May 28, 1959

Transplantation of the Ureters and Pregnancy

By Arthur Jacobs, P.R.F.P.S G.

Glasgow

This communication is an account of 4 patients from my personal series of ureterocolic anastomoses (Jacobs, 1957) who have borne children subsequent to the urinary diversion. The well-being of the mothers, 1 of whom has had 3 children, another 2, and the others 1 each, has not been adversely affected by the pregnancies. There was 1 fœtal death associated with a pregnancy which occurred eight years after the ureteric transplant. The other 6 children, the oldest of whom is now aged 13 years and the youngest 15 months, have all thriven. The following case histories describe the pertinent events in each:

Case I.—Mrs. J. M. Transplantation of the ureters to the pelvic colon by the Coffey technique was performed in January 1943, when the patient was 34 years of age. She had been incontinent as a result of two urinary fistulæ, one vesicovaginal and the other urethrovesicovaginal, sequelæ to a prolonged labour and forceps delivery of a first child, eight months previously. Two attempts at repair had proved unsuccessful and the referring gynæcologist considered that the prospect of effecting closure was remote. Duplication of the left ureter with crossing at the upper lumbar level was demonstrated on excretion urography and implantation of three ureters was accordingly required.

Three years later (1946), after an uneventful pregnancy, she was delivered by Cæsarean section of another baby girl. The obstetrician considered further child-bearing inadvisable and divided the fallopian tubes.

In January 1953, following repeated attacks of severe left renal pain, some with associated pyrexia, over the previous six weeks, urography showed no excretion from the left upper kidney segment. The renal attacks persisted and a left nephrectomy was carried out.

Now, sixteen years since the urinary diversion, she actively runs her household and leads a full social life. Rectal control is complete, with voluntary emptying at intervals of three hours and once at night. The pyelogram shows good concentration and a near normal outline in the solitary right kidney. The blood urea is 40 mg./100 ml. and the serum electrolyte figures remain within normal range. No medication for the maintenance of balance has been required.

Case II.—Mrs. J. Q. Transplantation of the ureters to the pelvic colon by the Coffey 1 technique was performed in May 1947, when the patient was 26 years of age. A vesicovaginal fistula had been present for a year and was a sequel to a forceps delivery of a dead-born fœtus after a prolonged labour. In spite of two attempts at repair, the fistula, which could readily admit two fingers, persisted.

A communication was received from a peripheral maternity hospital in March 1955 that a pregnancy commencing in May 1954 had proceeded without incident until the thirty-eighth week, when the fœtal heart stopped. A dead-born fœtus had been delivered by lower-segment Cæsarean section. When seen two months later she was having occasional left renal pain but otherwise felt well. On urography dilatation on the left side was noted. The blood urea was 51 mg./100 ml. and the serum electrolytes as follows: potassium 3·8, sodium 148, chloride 108·1 and alkali reserve 19·3 mEq./l. She was placed on potassium and alkali therapy. In May 1958, after febrile attacks associated with pain in the left renal region, an infected hydronephrotic left kidney was removed. Now she is fit and well and the serum electrolytes are normal.

Case III.—Mrs. A. H.—Transplantation of the ureters to the pelvic colon by the Coffey 1 technique was performed in March 1950, when the patient was 19 years of age. She had had urinary incontinence since the age of 3 years and 9 months, a sequel to a run-over accident which had resulted in a fracture of the pelvis with laceration of the external genitalia and urethra.

She married in November 1952, became pregnant in June 1953, and had an easy spontaneous delivery of a live mature female child weighing 5¾ lb. in February 1954. During the thirtieth week there was a transient attack of hæmaturia, attributed to a left-sided pyelonephritis, which disappeared in two days. Rectal urinary incontinence developed towards the end of gestation but control was regained on the first day after delivery. The puerperium was uneventful and the child progressed satisfactorily.

A second pregnancy followed four months later. The patient remained well and in March 1955, had spontaneous delivery of a live female child weighing 5½ lb. Progressive urinary incontinence, on this occasion starting in the second month, was again a feature, and as before, control returned immediately after delivery. The puerperium was uncomplicated and the child continued to thrive. Serum electrolyte examinations showed the sodium and alkali reserve a little below normal level and the chloride slightly elevated.

In August 1955 she was again pregnant. As the pregnancy progressed, she complained of shortness of breath on exertion and was unable to undertake her household duties. During the seventh and eighth months these symptoms became aggravated; improvement resulted from rest in an ante-natal ward. In May 1956, after a labour of eight hours, she delivered herself of a male child weighing 5 lb. The puerperium was uneventful and the patient was able to feed her child at the breast. The highest blood urea recorded during her stay in hospital was 34 mg./100 ml.

She reported in August 1956 complaining of slight pain in the left renal region and a persistent thirst. Urographic examination showed excellent concentration from both kidneys with a normal outline on the right side and moderate dilatation on the left. The serum electrolytes were: potassium 5·3, sodium 145, chloride 108·2, alkali reserve 22·2 mEq./l., blood urea 33 mg./100 ml. A low salt diet with alkali therapy was advised.

In the autumn of 1956 she was pregnant for the fourth time. She felt generally unwell, was easily tired, and rather fearful. The consensus of opinion after obstetrical and medical consultation was that the pregnancy should be terminated. Abdominal hysterotomy and sterilization was carried out uneventfully in December 1956. Now, nine years since the ureterocolic anastomosis, the dilatation in the left pelvi-calyceal system remains, but gives rise to no symptoms; electrolyte balance is readily controlled by alkali therapy.

Case IV.—Mrs. J. O. Transplantation of a solitary ureter to the pelvic colon by Nesbit's direct technique was performed in August 1953, when the patient was 16 years of age. When first seen a year earlier, she was suffering from incontinence due to urinary tuberculosis. Investigation then showed an advanced bladder contracture, widespread tuberculous disease in the right kidney and a marked hydroureter and hydronephrosis on the left side resulting from back pressure. A right nephrectomy, preceded and followed by tuberculostatic therapy (streptomycin and isoniazid) over a period of nine months, rendered the urine tubercle negative, but had no effect on the contracted state of the bladder or on the dilatation in the left kidney and ureter. When carrying out the urinary diversion the rigidity and calibre of the ureteric tube compelled a simple direct anastomosis, it being impossible to cover the implant with the seromuscular coats of the colon. With these conditions prevailing, the long-term prognosis was considered to be poor. The patient's general health quickly improved, however, and she married in 1955.

In May 1956 she was admitted to hospital from the ante-natal clinic in the eighth month of pregnancy. She was kept in hospital until term and had a normal delivery of a healthy girl. The puerperium was uneventful and the baby thrived.

A second pregnancy occurred in May 1957. On January 4, 1958, in the thirty-eighth week of gestation, following diagnosis of a breech presentation she was delivered by lower uterine Cæsarean section and sterilized. The baby, a boy weighing 5 lb. 13 oz., thrived and the puerperium was normal. She is at present on alkali therapy because of a persistently low alkali reserve but feels well and is actively running her household.

Discussion

The need for urinary diversion in non-malignant disease is tending to diminish because reconstructive surgery can now restore function to bladders formerly considered beyond rehabilitation. Though the intractable vesicovaginal fistula may still occasionally be encountered, most are amenable to repair either by the vaginal technique as advocated by Moir (1957) or by a transvesical approach such as that described by O'Conor (1957). For the contracted bladder due to tuberculous or other disease, ileocystoplasty is proving a most acceptable alternative and is now my procedure of choice for this condition.

Congenital anomalies, in particular vesical exstrophy, continue to call for urinary diversion. In a review of the literature, when reporting on Case III after the birth of the second child, Gordon (1956) found that out of the 23 cases of pregnancies subsequent to transplantation of the ureters brought to light, the operation had been carried out in 20 instances because of exstrophy of the bladder. One of the cases from Grey Turner's series had had three uncomplicated pregnancies and another recorded by Charles Mayo had given birth to twins (Turner, 1929; Mayo, 1919).

Conclusions

The obstetrician may occasionally encounter a pregnancy in a patient who has previously undergone transplantation of the ureters to the pelvic colon. As has been demonstrated by the above case histories, the pregnancy can generally be allowed to continue without expectation of serious added risk.

The urographic studies have shown that the dilatation which normally occurs in the upper urinary tract during pregnancy is not appreciably different after ureteric transplantation and that the usual resolution of this physiological modification can be expected. It is advisable, however, to be on the look-out for the onset of pyelonephritis and, in the event of an attack, to treat the patient by rest, copious fluids, alkalis, and chemotherapy or antibiotics if required.

Acknowledgments.—I am grateful for the co-operation of Dr. William Armstrong, Dr. John Hewitt, the late Dr. Donald McIntyre, and Dr. Robert Tennant who had the care of the patients during their pregnancies. I also desire to record my indebtedness to Dr. James Eaton, Dr. James Chambers, and Miss A. Dinwoodie, B.Sc., for the biochemical investigations and their aid to the problems of electrolyte balance.

REFERENCES

GORDON, W. J. (1956) *J. Obstet. Gynæc. Brit. Emp.*, **43**, 390.

JACOBS, A. (1957) *Brit. J. Urol.*, **29**, 307.

MAYO, C. H. (1919) In: Contributions to Medical and Biological Research, dedicated to Sir William Osler. New York: **2**, 1095.

MOIR, J. C. (1957) *J. Obstet. Gynæc. Brit. Emp.*, **44**, 362.

O'CONOR, V. J. (1957) Suprapubic Closure of Vesicovaginal Fistula. (Amer. Lect. Ser. No. 306.) Springfield, Ill.

TURNER, G. G. (1929) *Brit. J. Surg.*, **17**, 114.

Disinfection of Cystoscopes by Pasteurization

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Since it has been shown that the "antibiotic umbrella" affords no real protection against infection, or against cross-infection in hospitals, more attention is again being given to prevention by aseptic methods and the no-touch technique. No clinically acceptable antiseptic has been found which will disinfect ("sanitize") in a matter of minutes any instrument used on one patient to prepare it for use on another. Nothing less than boiling will do so for most purposes, and even this will not kill tetanus or anthrax spores, but the risk of infection of urological instruments by these spores is fortunately small. Nor will boiling kill the spores of many species of *Bacillus* (spore-bearing aerobes found in soil and dust) but these are not usually capable of establishing themselves in the urinary tract. Many antiseptics will kill bacteria on clean, smooth surfaces or in uniform experimental suspensions, but none suitable for clinical use will kill even non-sporing bacteria in blood clot, inspissated pus or tissue fragments unless given exposures of hours or days. The only established chemical sterilizing agents are ethylene oxide and formalin; both require several hours' exposure and expert supervision. It follows that non-boilable instruments should be eliminated from surgical practice as soon as possible.

Unfortunately many cystoscopes, resectoscopes and endoscopes will stand neither boiling nor exposure to alcoholic solutions, owing to the different expansion of glass and metal and the mechanical shock of cooling, or to the nature of the cement used in setting lenses and prisms in telescopes. It has been the usual custom to immerse such instruments in so-called antiseptic solutions; one commonly used is oxycyanide of mercury. The false reputation of mercurials as antiseptics is based on their bacteriostatic activity in very high dilutions which prevents the growth of living bacteria in prepared cultures. In recent years the inactivation of mercurials by sulphydryl compounds such as cystein, thiolacetic (thioglycollic) acid or even ammonium sulphide has shown that growth in culture can occur readily after treatment of bacteria with mercury compounds. Cationic detergents and chlorxylenols, also much used as disinfectants, are unreliable because of poor activity on coliform bacilli, particularly *Pseudomonas pyocyanea*, and all the common antiseptics may fail to penetrate blood clot in time to be of practical value, as I have shown experimentally. Tubercle bacilli are also resistant to many antiseptics, particularly when embedded in pus or sputum.

All non-sporing human-pathogenic bacteria, including *Mycobacterium tuberculosis*, are killed at 60° C. in 20 minutes or less in moist surroundings, except for *Streptococcus fæcalis* which requires 62°–65°. Shorter times are required if higher temperatures are used. In the pasteurization of milk the "holding" process requires 30 minutes at 61·7° C. (143° F.), the "high-temperature short-time" 15 *seconds* at 71·1° C. (160° F.). Accordingly I suggested that a few minutes' immersion in a water bath controlled at 70°–80° C. would be more reliable than any rapid chemical treatment. Most non-boilable plastics will withstand these temperatures without deformation or damage. The Genito-Urinary Manufacturing Company carried out trials with telescopes of non-boilable type and found they would withstand repeated heating at 80° C. and cooling from this temperature. A thermostatically-controlled water bath was constructed to the requirements of Mr. D. M. Wallace and he put it to clinical use.

Several experiments have been carried out to illustrate how readily non-sporing bacteria, even if enclosed in sealed tubes in the interior of a cystoscope, are killed by this method, and to show how difficult it is to kill with antiseptics even highly sensitive bacteria enclosed in blood. It has also been confirmed that tubercle bacilli are easily killed at 60° C.

Experiments

(1) *Streptococcus fæcalis* is the most resistant to heat of the recognized urinary pathogens, while *Pseudomonas pyocyanea* is the most resistant to antiseptics of the cationic detergent and chlorxylenol type. A strain of each was used for experiments in the water bath. Overnight peptone water cultures were diluted 1 in 50 in peptone water or nutrient broth, so as to contain 5–10 million viable bacteria per ml., and filled into capillary glass tubes of 3·5 mm. external diameter and 0·8 mm. wall thickness which were sealed. These provided a greater resistance to heat conduction than any likely layer of blood or pus on an instrument. Pairs of these culture tubes were heated in the water bath at various temperatures and times: 70° C. for 5 min. (6 pairs), for 10 min. (4 pairs) and for 20 min. (2 pairs); 75° C. for 5 min. and for 10 min.; 80° C. for 2 min. and 5 min. (2 pairs each). All remained sterile after two days' incubation. In view of this result still lower temperatures and shorter times were tested: 65° C. for 5 min. and 10 min.; 70° C. for 2 min. (2 pairs each). All remained sterile. Next a tube of each culture was slipped into a cystoscope from which the telescope had been removed. It was cooled in running tap water before each test. Sets immersed at 80° C. for 2 min. and 5 min. (2 sets each) from cold all remained

sterile. It would seem that total immersion in water at 80° C. for 5 min. or 75° C. for 10 min. would allow adequate margins.

(2) Heat resistance tests on *Mycobacterium tuberculosis* had to be done by a different technique, because of its cultural requirements and the hazard to laboratory staff. Liquid cultures of two strains were kindly provided by Professor Robert Knox. These were diluted 1 in 10 in Dubos liquid culture medium and 0·25 ml. volumes dropped into 2 x ½ in. tubes with drop-on metal caps. Subcultures after heating were made on Löwenstein-Jensen slopes. Unheated control cultures gave a semi-confluent growth of several thousand colonies easily visible in ten days. Cultures heated at 55° C. for 20 min., 60° C. for 10 min., 65° C. for 5 min., 70° C. for 2½ min. and 80° C. for 2½ min. all remained sterile after 1 month; those heated at 55° C. for 10 min. and 60° C. for 2 min. gave only a few discrete colonies not visible until after fifteen days' incubation.

(3) Several experiments were carried out with antiseptics. These followed the same basic pattern and the results are grouped together. Cultures in peptone water of *Strep. fæcalis* and *Ps. pyocyanea* were diluted about 1 in 50 in oxalated horse blood. Throat swabs of absorbent cotton wool on swab sticks were dipped into the blood, drained on the side of the bottle and dried for one to one and a half hours at 37° C. They were dipped into tubes or bottles of antiseptic solution or of saline in a water bath at the relevant temperature and were then cultivated in a tube of broth to which had been added thiolacetic acid to inactivate mercury salts, or in lecithin-Lubrol broth to inactivate chlorhexidine or domiphen bromide. Results are shown in Table I.

TABLE I.—TREATMENT OF BACTERIAL CULTURES IN BLOOD-IMPREGNATED SWABS WITH HEAT OR ANTISEPTICS

Treatment	Exposure time minutes	*Strep. fæcalis*	*Ps. pyocyanea*
65° C.	5	+	−
70° C.	5		
80° C.	2		
75% alcohol	1	+	−
	2	+	−
	5	+	+
5% phenol	2	+	+
	5	+	+
	10	+	+
5% Dettol	2	+	+
	5	+	+
	20	+	+
1 : 1,000 mercury oxycyanide	10	+	−
	20	+	−
	40	±	−
	60	−	−
1 : 8,000 mercury oxycyanide	20	+	+
	40	+	+
	60	+	+
	overnight	−	−
Chlorhexidine 0·02% aqueous	10	+	+
	20	+	+
	40	+	+
Chlorhexidine 0·5% in 75% alcohol	2	+	+
	5	+	−
	10	+	−
Domiphen bromide 1% aqueous	5	+	−
	10	+	−
	20	−	−

+ = growth. ± = reduced growth. − = no growth.

(4) Experiments with *Myco. tuberculosis* showed that although these organisms are resistant to many antiseptics, they are killed in less than 10 min. by 5% phenol or 0·5% chlorhexidine in 75% alcohol (Table II). In a separate experiment it was shown that the activity of the latter solution was entirely accounted for by the alcohol, which was shown to be effective by Smith (1947).

TABLE II.—SENSITIVITY OF A URINARY STRAIN OF *Myco. tuberculosis* TO SOME COMMON ANTISEPTICS

5% phenol	0·1% mercury oxycyanide	5% liquor chloroxylenols
2 min −	10 min +	5 min +
5 min −	20 min +	10 min +
10 min −	40 min +	20 min −
1% domiphen bromide	0·02% aqueous chlorhexidine	0·5% chlorhexidine in 75% alcohol
5 min + +	10 min + +	2 min + +
10 min + +	20 min + +	5 min + +
20 min +	40 min + +	10 min −
Controls	Lecithin-Lubrol broth + +	Thiolacetic acid broth + +

Fourteen-day liquid medium culture of a strain isolated from a case of renal tuberculosis. 0·5 ml. was added to 2·0 ml. oxalated horse blood, and 2 drops of the mixture were placed in sterile Kahn tubes. 0·5 ml. of antiseptic solution was added. At the end of the time of exposure 2 ml. of lecithin-Lubrol broth was added (or thiolacetic acid broth for mercury) and two drops subcultured after thorough mixing to a Löwenstein-Jensen slope.

Discussion.—The presence of dried blood, inspissated pus or tissue fragments will not interfere with the disinfecting or sterilizing action of heat, but may well impede the action of antiseptics under practical conditions of use. There is a vast literature on antiseptics and disinfectants; much of it is grossly misleading because the conditions of reported tests have not been related to conditions of use in practice, and this is illustrated by tests reported here. As stated in Appendix A on "Disinfection and Sterilization" in the Medical Research Council Memorandum No. 11 on "The Control of Cross Infection in Hospitals", sterilization by heat rather than by disinfectants should be employed wherever possible, since it is quicker and more reliable. In addition the M.R.C. War Memorandum No. 15 on "The Sterilization, Use and Care of Syringes" gives the opinion that the only chemical disinfectant that can be in any way recommended for syringe disinfection is 70–75% v/v alcohol, and then only when the syringes are used for no other purpose than the injection of a sterile fluid such as insulin in circumstances such that sterilization by heat is impracticable.

Summary.—Non-sporing pathogenic bacteria are all killed by moist heat at 65° C. or over in a matter of minutes. Non-boilable cystoscopes and similar instruments, which in many cases cannot be immersed in alcohol, can be satisfactorily disinfected for use by immersion in a constant temperature water bath at 80° C., in five minutes or 75° C. in ten minutes.

REFERENCE

SMITH, C. R. (1947) *Publ. Hlth Rep.*, **62**, 1285.

Mr. H. P. Winsbury-White: I feel that British instrument makers deserve the highest praise, when it is realized that the Genito-Urinary Manufacturing Company have been making boilable cystoscopes for the best part of thirty years; I personally have had

them in constant use for more than twenty-five years. Our gratitude for this triumph goes to the late Robert Schranz. It has long been a puzzle to me why these instruments do not seem to have been manufactured in other countries.

The crux of the difficulty is of course in being able to make a cement which is used for maintaining certain components of the optical system in their proper positions, and which does not melt with the heat. I emphasize that I have had these instruments in use for many years, without the heat interfering with their efficiency in any way.

I have always tried to keep to the boiling time of five minutes. For practical purposes, we must accept the fact that boiling is the best means we have so far of sterilizing cystoscopes. I would say that the pressure of work in outpatient clinics calls for this special equipment.

Anæsthesia for Urology

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Although there are many equally good ways of anæsthetizing a patient for urological surgery the physiological principles are, in the main, common to all and I propose to discuss the subject from this standpoint.

Since the surgical problems undertaken become increasingly complicated it is all the more important to strive for the production of good operating conditions, of which the two cardinal features are good surgical access and freedom from unnecessary bleeding.

In anæsthesia for retropubic prostatectomy and transurethral resection arteriolar and capillary bleeding can be reduced by the employment of good techniques and, in some cases, by the use of induced hypotension. In both these operations it is the venous bleeding which is most troublesome to the surgeon; it is difficult to control since it may be diffuse and it is prone to occur suddenly from a wide area. The only remedy for this complication is to tackle it from the systemic point of view, incorporating good anæsthetic technique with good positioning.

In most of our retropubic prostatectomies we have employed a light general anæsthetic combined with a muscle relaxant to which is sometimes added a small amount of volatile anæsthetic such as halothane. The combination of this drug with controlled respiration results in a considerable fall in blood pressure and it is seldom necessary to use other hypotensive agents as well. If it is decided, on the other hand, to employ a ganglion-blocking agent to reduce the blood pressure it is usually found that a much smaller percentage of halothane is necessary, but whichever method is used the end-results seem to be comparable. Forced ventilation from the start, by reducing the blood pressure, diminishes the blood loss considerably during the incision of the skin and subcutaneous tissue. It is important to ensure that muscular relaxation is complete; otherwise, despite the low blood pressure, the high inflation pressure which is necessary causes a back pressure in the large veins and so increases venous bleeding while producing a serious fall in cardiac output. Because of its vascular connexion, the prostatic plexus is particularly prone to engorgement under these conditions. If enucleation of the gland proves to be fairly easy it is not necessary to deepen the anæsthesia at this point, but when it is adherent to the capsule it may be advisable to protect the patient from traumatic shock by deepening the anæsthesia slightly, or by the use of intravenous pethidine. It is very striking how much more reflex shock occurs in younger patients than in older ones at this stage of the operation and this may be due to a degeneration of the autonomic nerve supply to the base of the bladder with advancing years.

Once the gland has been removed and a wedge of the trigone excised it is advisable slowly to return the blood pressure to a normal level. If this is done in close collaboration with the surgeon he is able to control the bleeding points one by one as they appear. The method of restoring the blood pressure to normal depends upon the anæsthetic technique which is being used. For this reason if atropine is to be used prior to a decurarizing dose of neostigmine this is a good point in the operation at which to give it, since the resultant tachycardia is almost always followed by a significant rise in blood pressure. If this is followed by a reduction in the concentration of halothane the blood pressure may return to normal but, where necessary, a small dose of a vasopressor such as methylamphetamine can be given intravenously.

There is a wide diversity of opinion regarding transfusion during prostatectomy as many factors have to be taken into account. In elderly patients with a poor cardiovascular system post-operative hypotension may be dangerous as it predisposes to coronary infarction and cerebral ischæmia. In healthier people, in whom there has been no great loss of blood,

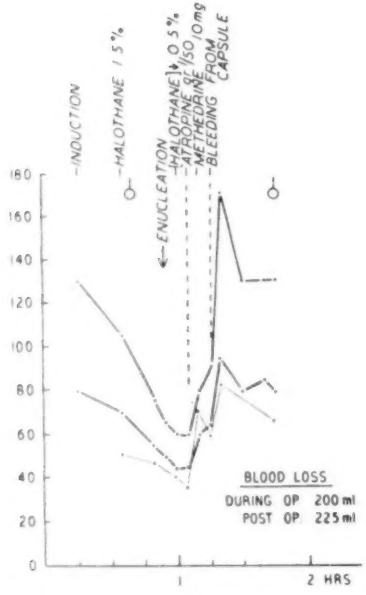

FIG. 1.

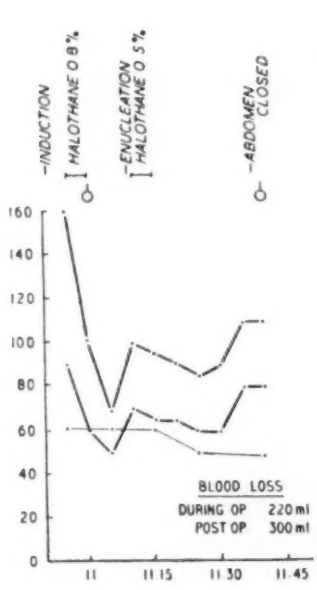

FIG. 2.

Figs. 1–4 are four typical anæsthetic charts recorded during retropubic prostatectomy (blood pressure in heavy lines, pulse-rate in faint line). The symbol ♁ demarcates on the time-scale the beginning and end of the operation.

there would seem to be a definite advantage in withholding intravenous fluids as these undoubtedly predispose to post-operative bleeding. I have often seen grave complications due to post-operative clot retention but I have never seen a patient's life jeopardized through lack of transfusion after a prostatectomy. This is, of course, a matter of experience and little harm is done by starting a slow saline or glucose infusion at the beginning of the operation so that blood can be substituted at a moment's notice when this is necessary. It is, of course, most important not to wait so long that one is obliged to transfuse rapidly, as this will almost certainly lead to post-operative bleeding.

I cannot emphasize too much the importance of restoring the blood pressure to normal before the cystoscope is removed after transurethral prostatectomy. In connexion with this, an injection of adrenaline into the gland before endoscopic resection of the prostate renders the patient liable to post-operative bleeding when the effect of this drug has worn off.

There are several methods of regional blocking, such as epidural anæsthesia and the method of retropubic infiltration described by Ellis and Leatherdale (1958). Regional anæsthesia may be used with or without the addition of a light general anæsthetic and results in very good operating conditions with a conspicuous lack of bleeding. If an epidural catheter is left in position post-operatively the analgesia can be continued by repeated small injections, giving rise to a very tranquil recovery period when the patient sleeps peacefully instead of becoming restless and attempting to pull out his catheter. One disadvantage of this method, however, is that it requires a specialized post-operative nursing technique; otherwise a prolonged and dangerous hypotension may ensue.

Subarachnoid block by low spinal anæsthesia gives excellent results in experienced hands but this method has, quite undeservedly, fallen into disrepute. One reason for this is that, even in the best surgical hands, the patient may have a period of post-operative sphincter disturbance and where spinal anæsthesia has been used one can never be certain that this was not a contributing factor.

Very good results have been produced in anæsthesia for prostatectomy using large doses of chlorpromazine combined with nitrous oxide-

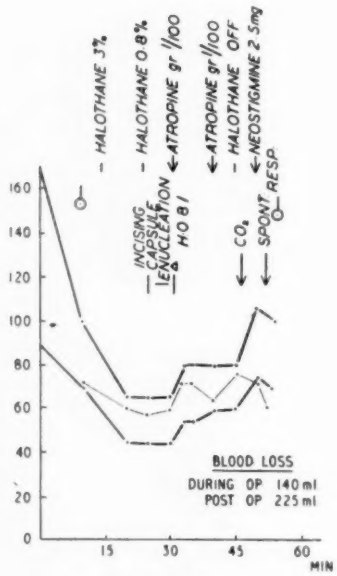

FIG. 3.

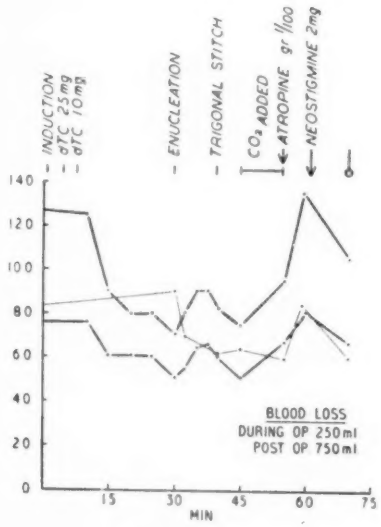

FIG. 4.

oxygen and a relaxant. These cases do very well but are prone to alarming periods of post-operative hypotension which may be undesirable.

Anæsthetic risks in prostatectomy.—It is very noticeable how well these patients do despite their age group and the very common respiratory and cardiovascular complications with which they present. Death during the operation is very rare, but it is on the second or third day that the subject is in his most critical state and this is one of the reasons for avoiding transfusion as much as possible. For this reason I feel very strongly that a patient's physical condition alone should never be the reason for performing transurethral resection in preference to a retropubic prostatectomy, because the post-operative course of the former operation is often far more worrying than that of the latter, even in the most skilful and experienced hands. Obviously where there is some surgical consideration, such as carcinoma of the prostate, transurethral resection is the method of choice, but there is a great deal of evidence that, from the anæsthetic aspect, a patient who is fit for a transurethral resection is also fit for a retropubic operation.

Candidates for cystoscopy usually present little problem to the anæsthetist, but occasionally this procedure is necessary in someone who is gravely ill. The type of complication will determine the choice of anæsthesia, which may vary from caudal block or topical anæsthesia to a light general anæsthetic, using an agent such as cyclopropane which is eliminated very rapidly as this diminishes the post-operative risk. Where retrograde pyelography is contemplated all that is necessary is a light general anæsthetic during which a short period of apnoea is produced during the exposure of the X-ray film. The simplest way to achieve this apnoea is to over-ventilate the patient for about one minute on a closed circuit with CO_2 absorption. This produces acapnœa so that the patient does not breathe again for about 20 seconds. It is seldom necessary to use muscle relaxants or large doses of thiopentone.

Where there is a risk of explosion due to the X-ray apparatus, halothane is an excellent substitute for cyclopropane.

If it is desired to collect ureteric specimens during pyelography it is important to avoid morphine and pethidine derivatives pre-operatively as these drugs suppress renal secretion.

REFERENCE

ELLIS, H., and LEATHERDALE, R. H. L. (1958) *Lancet*, ii, 1189.

Meeting
June 25, 1959

MEETING AT THE MEDICAL COLLEGE OF ST. BARTHOLOMEW'S HOSPITAL, LONDON

A Feminizing Tumour of the Testis

By P. PATON PHILIP, M.Chir., F.R.C.S.

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CASE HISTORY

The patient, a man of 22 years, was admitted to hospital 25.7.58. Two years before he had noticed discomfort in the breasts, especially on the left, associated with slight swelling. This persisted. One year before he was treated by his private doctor with testosterone injections and the swelling of the breasts subsided. Just before admission to hospital he complained of diminution in the size of the left testicle with some loss of hair from the chest and pubic region.

When seen as an out-patient the left testicle was slightly smaller than average. The right testicle was slightly larger and what was thought to be a small tumour was palpable in the body of the testis and a small vaginal hydrocele was present. Both breasts were found to be slightly enlarged, the left more than the right, and pigmentation was present around the areola. He also admitted in retrospect to some loss of libido. Nothing else of note was reported.

The Aschheim-Zondek test was negative and 17-ketosteroids were within normal limits, being 12·7 mg.% in twenty-four hours.

On 28.7.58 the right testicle was explored. The testis itself looked relatively normal and no definite tumour could be demonstrated. A small piece of testis taken for section from the area where the tumour was thought to be palpable showed a Leydig cell tumour. Fluid from the hydrocele was found to contain solid clumps of interstitial cells. A few days later a right orchidectomy was performed and on slicing open the testicle a spherical, encapsulated tumour, 2–3 cm. in diameter was seen. Section confirmed a typical interstitial cell tumour with no evidence of malignancy.

At follow-up two months later the left testicle had become larger in size, and the patient seemed to have been right in his original observation that his left testicle had become smaller. He had grown more hair on his chest and pubic region. His libido had returned to its previous normal. A hormone survey showed the following results: Œstrone 7·6, œstradiol 2·9, œstriol 14·9 μg.; total 25·4 μg. This value would appear to be elevated as the upper limit of normal for an entire man is usually considered to be about 15 μg.

A further hormone survey was performed on his urine at the Royal College of Surgeons on June 12, 1959, and the results were almost identical with the previous one. The œstrogens remain markedly raised, although the patient is entirely symptom free.

It would seem therefore that some deep seated œstrogenic mischief is afoot, with nothing so far to account for it.

Discussion.—The first case was reported by Sacchi in 1895; I have found 51 additional examples described in humans. The condition has also been reported in various species of animals.

From the U.S.A., in a well-known survey of 10 million servicemen, Broughton reported the finding of 1,000 testicular tumours of which 9, or 1% of cases, were interstitial cell or Leydig cell tumours.

The youngest case reported was 1½ years old and the oldest was 82. Two malignant cases were reported, dying with metastases four and ten years after orchidectomy respectively.

There seem to be two distinct varieties reported in humans, prepuberal (17 cases) and postpuberal (34 cases). In the prepuberal cases, where the average age was 5 years, almost invariably symptoms of sexual precocity were present. The children were well and prominently endowed with external genitalia and their symptoms and behaviour were the subject of alarm among their parents. In some the opposite testis was enlarged and most developed the typical male deep voice although of tender years. In the majority complete retrogression of symptoms followed orchidectomy. Most tumours were right sided and one case was bilateral.

In the postpuberal cases, the symptoms were entirely different. None was reported of increased virilism although one was found by hormone survey to be excreting large amounts of testosterone. Most occurred about the age of 30. Of 25, 13 were left sided, 9 right sided and 3 bilateral. In 11 of the 25, adults, there were no symptomatic endocrine disturbances. The tumours were found incidentally at post-mortem examination, or at operation on undescended testicles, or presented with enlargement of the testicle.

In the remainder, which was the larger group,

hormonal changes were present, but entirely different from those found in children.

Gynæcomastia was present in 7 patients, impotence in 4, and decreased libido in the rest. The response to orchidectomy in adults was usually a return to normal with return of libido and disappearance of gynæcomastia. In one case, the remaining testicle increased in size after orchidectomy, as in our patient.

It should be emphasized here that although the hormonal effects of the tumour before puberty are so different from those occurring after puberty, the histological picture of the tumour in all cases including animals is the same and is usually as follows:

The tumour, which is well encapsulated and 2·3–2·5 cm. in diameter, consists of nests and cords of eosinophilic cells set in a loose myxomatous stroma. Cytoplasm is vacuolated. Nuclei and nucleoli present. Scanty nuclear cytoplasm which is finely granular. Mitoses rare. The cells are arranged in a pattern strongly suggestive of liver cords loosely scattered in myxomatous stroma. Aggregates of lymphocytes and brownish coloured granules of lipofuchsin are present.

It seems odd that apparently identical tumours should be responsible for such different effects in the two age groups. It might be expected that the interstitial cells would produce testosterone or some similar hormone.

The literature is full of possible explanations, both likely and unlikely. One suggestion was that the tumours producing feminizing effects in adults were really Sertoli cell tumours and Sertoli cells in the testis are supposed to elaborate œstrogen (Lewis and Stockard, 1950). However, Sertoli cell tumours have been described but rarely in humans, and even then their existence has been regarded with some scepticism. They are reputed to be quite common in animals.

Some authors suggest that the anterior pituitary is at fault and produces some form of œstrogen excess which causes the formation of the testicular tumour and the gynæcomastia, impotence and loss of libido. This sounds unlikely, but there is no doubt that experimentally in animals œstrogens cause tumour formation in the testis with typical interstitial cells.

Many experiments have been performed using different œstrogens with the same result. Bonser and Robson (1940) used œstradiol diproprionate. Hooker *et al.* (1940) produced typical interstitial cell tumours with metastases in mice with œstradiol benzoate injections. Shimkin and others produced the same effect in mice with implants of stilbœstrol pellets. McCullagh and Rossmiller (1941) reported gynæcomastia in males who had received large doses of testosterone. The condition retrogressed when the hormone was discontinued. Twombly *et al.* (1949) found that anterior pituitary extract caused interstitial cell hyperplasia and gynæcomastia in animals. In one case of interstitial cell tumour in an adult, marked elevation of urinary gonadotrophin was found (Reiners and Horn, 1949). Hunt and Budd (1939) found positive pregnancy tests in a typical Leydig cell tumour without any obvious trophoblastic tissue present in the tumour. In one 5-year-old child with a Leydig cell tumour the hormone was identified as 3-hydroxy-17-ketosteroid and this was said to fit the pattern of androsterone (Cook *et al.*, 1952).

Cohen (1946) stipulated adrenal rests. Interstitial cell tumours closely resemble androblastomata. Hormonal changes of gynæcomastia and impotence resemble to some extent rare cases of adrenal cortical tumours in men producing feminizing symptoms.

Pierce *et al.* (1957) transplanted human chorionic carcinomas and teratomas into the cheek pouch of cortisone-treated hamsters; sera from the hamsters were used for hormonal assay and the tumours were transplanted through many generations. Perhaps Leydig cell tumours could be similarly investigated.

Acknowledgment.—I wish to convey my thanks to Mr. A. W. Badenoch for his help and permission to publish this case.

REFERENCES

Bonser, G. M., and Robson, J. M. (1940) *J. Path. Bact.*, **51,** 9.

Cohen, H. (1946) *Amer. J. Path.*, **22,** 157.

Cook, C. D., Gross, R. E., Landing, B. H., and Zygmuntowicz, A. S. (1952) *J. clin. Endocrin.*, **12,** 725.

Hooker, C. W., Gardner, W. U., and Pfeiffer, C. A. (1940) *J. Amer. med. Ass.*, **115,** 443.

Hunt, V. C., and Budd, J. W. (1939) *J. Urol.*, **42,** 1242.

Lewis, L. G., and Stockard, C. G. (1950) *J. Urol.*, **64,** 518.

McCullagh, E. P., and Rossmiller, H. R. (1941) *J. clin. Endocrin.*, **1,** 496.

Pierce, B., Dixon, F. J., and Verney, E. L. (1957) *Cancer Res.*, **17,** 134.

Reiners, C. R., and Horn, R. C. (1949) *Amer. J. clin. Path.*, **19,** 1039.

Sacchi, E. (1895) *Riv. sper. Freniat.*, **21,** 149.

Twombly, G. H., Meisel, D., and Stout, A. P. (1949) *Cancer*, **2,** 884.

Sacral Agenesis and Micturition

By D. F. Ellison Nash, F.R.C.S.

London

Co-existing neurological maldevelopment and primary visceral anomaly justify attention being called to this condition.

Williams and Nixon (1957), Friedman (1950) and I myself (Nash, 1957) have done so previously.

Various classifications have been put forward. I would use the term *sacral dysplasia* to include:

A. *Primary defects*
- (i) Sacral agenesis, complete or partial (Fig. 1).
- (ii) Sacral dysgenesis: hemisacrum, scoliosis, bifidum or fusion and *primary* hypoplasia (Fig. 2).

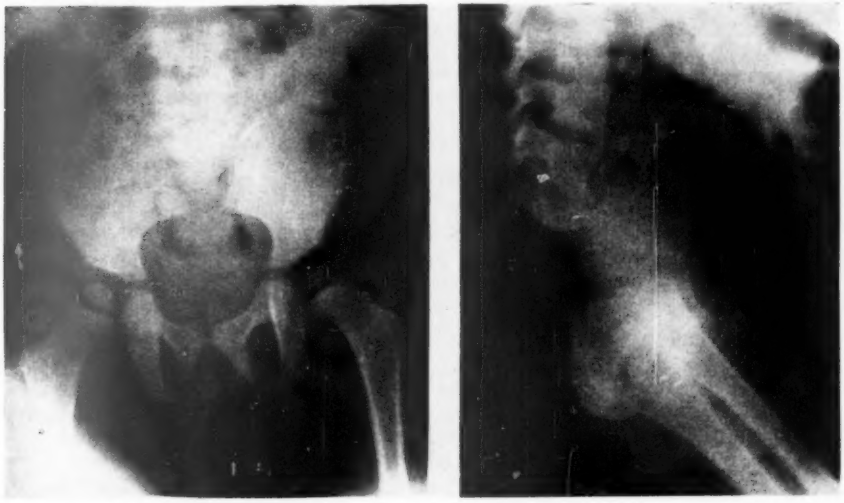

Fig. 1.—Anteroposterior and lateral radiographs to show agenesis of all except the first piece of sacrum.

B. *Secondary defects*

Paralytic hypoplasia, Paralytic scoliosis } usually with spina bifida cystica at a higher level.

The purpose of distinguishing this group from other spinal defects is to emphasize three points:

(1) A considerable number of children and adults with this condition have so little locomotor defect that the primary disability is overlooked until urinary infection or incontinence supervenes (6 out of 16 in this series).

(2) The condition is frequently associated with congenital dysplasia of those viscera which arise solely or in part from the urogenital sinus or wolffian duct, i.e. anorectum, urinary tract (Fig. 3). Thus treatment for the primary visceral defect may overlook the fact that the whole pelvic floor is mechanically (structurally) defective and both viscerosensory and visceromotor innervation is impaired or absent. 8 out of 16 in the present series had such visceral anomalies: this compares with a similar finding of 28% and 31% in two other recorded series. Williams and Nixon (1957) further noted that out of 41 children with imperforate anus, 12 had sacral agenesis.

(3) The discovery of sacral absence or abnormality demands full urological investigation whether or not any neurological deficit can be detected. The condition should be found in routine neonatal examination, but may be discovered fortuitously during rectal examination if one can ensure that the examining finger registers what it does not feel, as well as what it feels!

Some cases of agenesis are accompanied by spina bifida or present the same total clinical problem; others have very little disability apart from the urological problem. Only 1 out of my

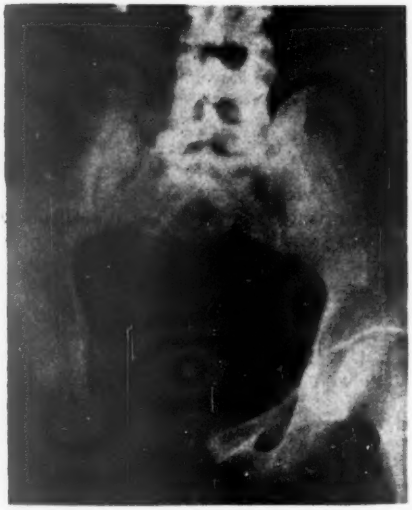

FIG. 2.—Primary hypoplasia and scoliosis associated with spina bifida occulta. The only overt physical abnormality was pes cavus, until retention with overflow incontinence developed at the age of 28.

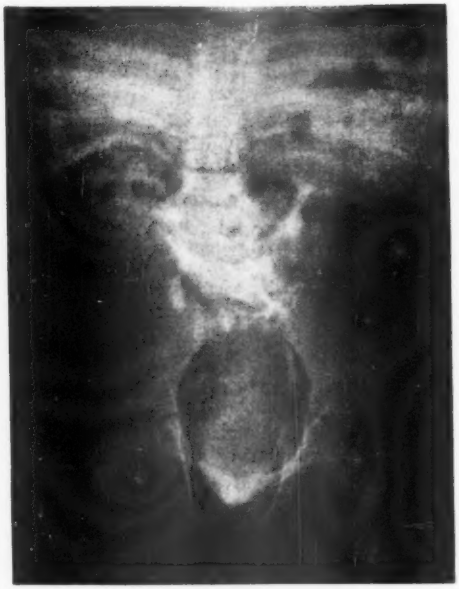

FIG. 3.—Sacral agenesis with pancake low lumbar kidney.

16 has any congenital abnormality (a cleft palate) outside the axial skeleton, including ribs, and the recto-urinary derivatives. Fused vertebræ, fused ribs and Arnold-Chiari cerebellar malformation have occurred, but these are all axial.

The neurological problem is very bizarre. I have found very little gain from cystometric investigations though I admit that for academic reasons they should perhaps be included. The management of these cases differs very little from the management of paraplegic incontinence in spina bifida, but more often the case of agenesis has a useful amount of visceral sensation.

Boys with a minimal paralysis may be made dry by urethral plication. Both boys and girls have required bladder-neck resections as life-saving measures.

REFERENCES

FREEDMAN, B. (1950) *Brit. J. Surg.*, **37**, 299.
NASH, D. F. E. (1957) *Ann. R. Coll. Surg. Engl.*, **20**, 349.
WILLIAMS, D. I., and NIXON, H. H. (1957) *Surg. Gynec. Obstet.*, **105**, 84.

The following papers were also read:

Hyperoxaluria.—Dr. E. F. SCOWEN. *See:* Hyperoxaluria. Lectures on the Scientific Basis of Medicine. London; Vol. 8 (in press).

Preliminary Report on the Use of the Cobalt Bomb for Neoplasm of the Bladder.—Dr. W. M. LEVITT.

Sex Hormones and Behaviour of Birds.—Dr. A. J. MARSHALL. *See:*

LOFTS, B., and MARSHALL, A. J. (1959) *J. Endocrin.*, **19**, 16.
MARSHALL, A. J. (1954) Bower Birds. Oxford.
——, and SERVENTY, D. L. (1957) *Proc. zool. Soc. Lond.*, **127**, 489.
——, —— (1959) *Nature, Lond.* (in press).
——, and WILLIAMS, M. C. (1959) *Proc. zool. Soc. Lond.*, **132**, 313.

BOOK REVIEWS

The Mast Cells. By James F. Riley, M.B., Ch.B. (Hons.), M.D., Ph.D., D.M.R.T., F.R.C.S.E. (Pp. x + 181; illustrated 30s.) Edinburgh and London: E. & S. Livingstone Ltd. 1959.

This book has been written by the leading authority on mast cells. There is a foreword by Sir Henry Dale, then Dr. Riley reviews the literature from the time of the discovery of mast cells by Ehrlich in 1879 to the development of the view that mast cells form heparin which serves as a natural anticoagulant. The main section of the book deals with experimental work carried out by the author, at first alone, and later in a happy association with Dr. G. B. West. They were the first to reveal the close relationship between the number of mast cells and the histamine content of tissues. This holds not only for normal tissues but also for pathological states such as urticaria pigmentosa in man and mast cell tumours in animals. They showed also that histamine-liberators caused the mast cells to disintegrate and release the histamine contained in their granules. Dr. Riley discusses the way in which histamine is held in the granules in association with heparin and proteins and the possible mechanisms of its release. He does not accept the view that heparin is normally released into the blood stream. Dr. Riley suggests that released heparin is retained locally and that the natural function of the mast cell is to store and release mucopolysaccharides for the connective tissues.

This book is an excellent account of recent original work in a still developing field.

Major Endocrine Disorders. By S. Leonard Simpson. 3rd edition, with the collaboration of A. Stuart Mason and G. I. M. Swyer. (Pp. vi + 459; illustrated. 50s.) London: Oxford University Press. 1959.

This book running to 459 pages in fact discusses more than major endocrine disorders and must rank as a textbook of endocrinology. Unfortunately the level of discussion is often uneven. For example the excellent concise section on adrenal steroids is only likely to be comprehensible to the biochemically orientated endocrinologist whereas that on radioactive iodine is pitched at a much lower level for third-year medical students. Endocrinology is not easily understood when there is over-emphasis on syndromes, and this book would be much more acceptable if the principles and mechanisms involved were more clearly presented. The pituitary may be the conductor of the endocrine orchestra, but for the student it is often better to start with the individual instruments rather than concentrate initially on the complicated activities of the figure on the rostrum. Nor is the reader likely to be enlightened by such a sentence as "In young boys with hypogonadism, in which condition gonadotrophins—which produce testosterone—or testosterone itself may be indicated, the hormone is usually administered with caution, because of the theoretical possibility of premature union of the epiphyses, but in actual practice in man this does not appear to occur, and, in fact, skeletal growth appears to be appreciably accelerated".

A Pocket Book of Proprietary Drugs. Compiled by Alistair G. Cruikshank, F.R.C.P.E., and Cornelius Stewart, L.R.C.P.&S.E., M.P.S. (Pp. 236. 10s. 6d., interleaved copy 14s.) Edinburgh and London: E. & S. Livingstone Ltd. 1959.

This gives a short account of the composition, indications and general properties, dosage and packs of some fifteen hundred proprietary preparations available in this country based on their manufacturer's statements. Handy in size, there is enough information to assist the practitioner in his selection of drugs. Even this summary has its addendum, a significant comment on the rate of increase in new preparations. Only preparations for prescription are described, none advertized to the public is included. It will save labour in the identification of drugs and their prescribing and is as up to date as is humanly possible. The authors have done a useful piece of work.

A Laboratory Manual of Chemical Pathology. By Professor F. T. G. Prunty, Dr. R. R. McSwiney and Dr. Joyce B. Hawkins. (Pp. ix + 260; illustrated. 35s.) London, etc.: Pergamon Press. 1959.

This is not an exhaustive textbook of methods but a practical handbook discussing in detail the authors' own preferred techniques. The first 52 pages give concise and useful practical information on standard solutions, quality control, metabolic balance experiments, clearances and clearance rates and body fluid volumes. Sections on colorimetry, flame photometry and pH wisely consider general principles and not details appropriate for specialized instruments, but three and a half pages can hardly do justice to paper chromatography. The main part of the book describes the principle, necessary reagents, technique and calculation for seventy-three different measurements and is sufficiently comprehensive to include blood ammonia, citrate, galactose tolerance, inulin and fructose, pyruvate tolerance,

porphobilinogen and porphyrin and the vitamin-A absorption test. The rapid tablet and strip qualitative tests for urine are also described. It is remarkable, however, that the recently developed estimations of enzyme activity in plasma are omitted. The more convenient methods now available for salicylate, phosphatase and fæcal fat are not described and the authors recommend the estimation of total and split fat in dried stool. The account of the determination of protein-bound iodine does not sufficiently emphasize that exceptional facilities are necessary to avoid contamination. The micro-Kjeldahl procedure is described in full, instead of the numerous less satisfactory shorter methods. Although no attempt has been made to consider interpretation, this well-produced manual can be recommended for use in every chemical pathology laboratory.

Elementary Medical Therapeutics. By G. F. Walker, M.D., F.R.F.P.S.(Glas.), D.C.H., M.R.C.P.(Lond.). (Pp. 69. 7s. 6d.) Bristol: John Wright & Sons Ltd. 1959.

The author has preferred to deal with a relatively small number of the possible methods of treatment on the assumption that adequate depth is better than inadequate breadth of information. Such a selection has naturally a bias of personal preference and experience but it will be useful for senior medical students and housemen. The contents are arranged alphabetically and are accompanied by useful comments on the indications and contraindications of the various therapeutic measures suggested.

Treatment of Cancer and Allied Diseases. Edited by George T. Pack, M.D., F.A.C.S., and Irving M. Ariel, M.D., F.A.C.S. Vol. 2: Tumours of the nervous system. (Pp. xvii + 316; illustrated. £5 5s.) London: Pitman Medical Publishing Co. Ltd. 1959.

This volume, the second in the series on the Treatment of Cancer and Allied Diseases, contains twenty-one articles, all but two from North American authors. The contributions cover with considerable variation in detail and complexity most aspects of tumours of the central and peripheral nervous systems. On the credit side it is lavishly produced with really excellent photographs and illustrations. It is reasonably up to date in most of its material, a difficult feat in a branch as dynamic as this. Of great interest to British readers will be a preliminary account of neutron capture therapy from Farr of Brookhaven. Inevitably it has all the defects of such a symposium. There is considerable overlap and redundancy between several of the articles. Often quite contrasting opinions are stated dogmatically and without reservation in succeeding contributions. There is considerable variation between articles in the standard aimed at—in other words it is not clear for what level of reader this volume is intended. Individually, practically every contribution is good, one or two first-rate. The effect of them as a whole in one volume is rather blurred, suggesting that this is intended as a reference book rather than to be read through. It would benefit, even so, if the editors took upon themselves more dictatorial powers.

A Textbook of Medicine. Edited by Russell L. Cecil, M.D., Sc.D., and Robert F. Loeb, M.D., Sc.D., D.Hon.Causa, LL.D. 10th ed. (Pp. xxxiii + 1664 + lxxxix; illustrated. £5 15s. 6d.) Philadelphia and London: W. B. Saunders Company. 1959.

This tremendous book has now reached its 10th edition. It is one of the very large textbooks of medicine for which the United States is justly famous, and almost the whole of medicine is covered by articles from world-famous authorities, including in this edition Sir Russell Brain.

Medicine is too vast to allow a single volume to cover all its aspects, even at a relatively elementary level, and in this one discussion of differential diagnosis is sometimes sacrificed. It is, however, a book of reference which senior students and practitioners with a thirst for concentrated information will find gives them a great deal of what they require. It is also especially suited to the smaller hospital libraries, where the number of volumes is perforce limited, as it contains a vast amount of information for a surprisingly reasonable price.

The School Health Service. By S. Leff, M.D., D.P.H., Barrister-at-Law, and Vera Leff. (Pp. viii + 316; 30s.) London: H. K. Lewis & Co. Ltd. 1959.

The school health and dental services of local educational authorities are described in some detail, though relatively little space is given to the ascertainment and education of handicapped pupils. The emphasis throughout is upon the past, almost half the contents being devoted to the historical development of the school health service during the first part of this century when social conditions were less favourable than they are to-day. Only brief consideration is given to the ways in which the service may be adapted to meet future needs. The authors are mainly concerned with the contribution made by medical services to the health of children of school age, rather than with the relation of health and physique to education. This seems unfortunate since with a comprehensive National Health Service the retention of a

separate school service may be justified to an important extent on educational grounds. The medical supervision of children in private schools is not referred to.

It is doubtful whether students of public health and doctors doing school health work will find in this book a sufficiently critical examination of the various school health activities for their purposes, though this deficiency is offset to some extent by a useful list of over 200 references. School nurses and social science students may find the book of more value.

Pathophysiology in Surgery. By James D. Hardy, M.S.(Chem.), M.D., F.A.C.S. (Pp. xx + 704; illustrated. 152s.) London: Baillière, Tindall & Cox, Ltd. 1958.

A cynic might well claim that there was no such subject as surgical pathology and that surgical physiology was a contradiction in terms; be that as it may this book makes an honest attempt to provide a background for the student of surgery. If he has been denied a proper introduction to the basic sciences, then he will welcome such a volume as this and any surgical apprentice would find it a most valuable textbook. It represents one man's attempt to write down the why and wherefore behind most modern surgical treatment, is written clearly and is beautifully illustrated.

Some sections are dealt with much more thoroughly than others and one can tell what are the author's special interests. The book is by no means up to date and such subjects as the auto-immune bodies find no place in it. The references are almost exclusively to the American literature, but probably the students for whom the book was originally written will not have access to any other. This volume has been beautifully printed and produced.

Skin Diseases in the African. By G. H. V. Clarke, M.A.(Cantab.), M.B., B.S., A.R.I.C. (Pp. 172; 261 illustrations. £4 4s.) London: H. K. Lewis & Co. Ltd. 1959.

A book on diseases of the skin in the dark-coloured races has been a long-felt want, for a physician going from Western countries to Africa finds considerable difficulty in accustoming himself to the alteration of the appearance in common skin diseases in the dark skin. Dr. Clarke is to be congratulated on producing a book of this nature at the modest price of £4 4s.

The whole range of dermatology is almost completely covered. It is inevitable, in a book which is largely devoted to illustrations, that the descriptions have to be considerably curtailed. Particularly is this the case in the chapter on the histology and physiology of the African skin. This could have been expanded to advantage.

The photographs generally are good, but some would have been better omitted or replaced, and it is surprising that nodular leprosy, of which there must be a large number of photographs, is so poorly illustrated. Illustration No. 128 is also somewhat confusing, and is apparently a mixture of several conditions. Nos. 137 to 139 would also puzzle the young practitioner, but are of value in the fact that they remind him that irritative dermatitis may have an onchocercial basis, and this condition should always be borne in mind.

A very valuable section of the book is the bibliography which appears to be very full indeed, and should be most helpful. The general presentation is good. The whole book must be accepted as an illustrative skin atlas devoted to the photographic appearance of skin diseases in the African. This book should be on the shelf of all those who have, from time to time, dermatological conditions to differentiate, not only in the African but in the darker races throughout the world.

Gynecologic Radiography. By Jean Dalsace, M.D., and J. Garcia-Caldéron, M.D. (Pp. xvii+188; illustrated. 60s.) London: Cassell and Company Ltd. 1959.

This book has been translated in New York by Hans Lehfeldt from a work by the French authors Jean Dalsace and J. Garcia-Caldéron. Since the atlas has gained some renown amongst French radiologists, the publishers have done a service in making it available to the English-speaking reader.

Containing a minimum of text but enough adequately to explain the many radiographs illustrated, the collection includes most of the more common and a number of the less common morbid conditions displayed by opaque media in the female genital tract. Opaque oil has been used largely in the cases illustrated but some examples of water miscible media are included and their value assessed. The atlas makes it evident that a hystero-salpingogram will provide information beyond the simple estimate of tubal patency and can be of real service in the detection of early tumours in the uterus and adnexa.

A weakness of the work is the mixture of positive and negative prints which for some readers is a source of irritation.

British radiologists and gynæcologists will find a perusal of this atlas stimulating and a reminder that possibly the full value of hystero-salpingography has not been realised.

A chapter on radiography of the breast by Charles M. Gross and Robert Sigrist has been included.

Children in Practice. By John Peterson. (Pp. vii + 226. 25s.) London: Cambridge University Press. 1959.

It is difficult for the medical student, trained and taught in hospital, to appreciate the social problems of child patients seen in the artificial environment of hospital. This book should become a standard work, not only benefiting the student and general practitioner, for whom it is primarily intended, but proving salutary reading for all connected with child care at home and in hospital.

The book begins with a somewhat lengthy account of environmental factors influencing the child at home, at school, and in the neighbourhood in which he lives. References are made to published work on the subject and apt quotations given. Difficulties in understanding and treating problems far removed from personal experience are lucidly illustrated by case histories.

The final chapters contain a wealth of factual material concerning maternity and child welfare services, school health service, and the care of mentally and physically handicapped children.

This volume should prove of inestimable value in bringing about a fuller understanding of social problems affecting the child's health and development. The examination-ridden student and the busy practitioner may find it rather lengthy, but they can be assured that time given to its study will be well spent.

Temporal Lobe Epilepsy. A Colloquium sponsored by the N.I.N.D.B. Eds.: Maitland Baldwin and Pearce Bailey. (Pp. xiii + 581; illustrated. £5 17s. 6d.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

Interest in the temporal lobe and the part that it may play in epilepsy has been intense and world wide, and in 1954 an international discussion on epilepsy took place in Marseilles, organized by Professors Morin and Gastant. Attention became focused on the temporal lobe, and it was decided to hold another meeting in 1957. The volume under review is a report of the papers and discussions at that meeting which took place in Bethesda. The contributors are all outstanding in this field of work and deal with the subject from all angles. Thus everyone interested in epilepsy will find something of special value in this volume, and for the neurosurgeon it may be considered essential, if he wishes to be abreast of the latest techniques. He will find much discussion and profuse illustration of electrocorticography, and of implanted electrodes, though he will probably be somewhat dismayed by the variety and detail of tabulated analyses; he will wonder whether, in some, the numbers of cases are sufficient to warrant conclusions. The results of surgical removal of portions of the temporal lobes, so far as the epilepsy is concerned, are fairly uniform; about two-thirds are greatly benefited, the attacks ceasing or being reduced to one or two a year. It is a challenge that no one has done better than this, and such results were nearly attained before the EEG was invented. Whether psychiatric troubles were curable gave rise to much difference of opinion, though some patients seem indubitably to benefit. It is likely that the type of disturbance is all-important. What is not apparent from the colloquium is general agreement as to what constitutes "temporal-lobe epilepsy", and what are the strict criteria for operation. As Dr. Percival Bailey remarks: "It seems that we may look confidently forward to a third colloquium."

The book is excellently produced, the illustrations are clear, and there are ample references. Although expensive, it is good value.

That the Patient May Know. An Atlas for Use by the Physician in Explaining to the Patient. By Harry F. Dowling, M.D., Sc.D., and Tom Jones, B.F.A. (Pp. xiii + 139; profusely illustrated. 52s. 6d.) Philadelphia and London: W. B. Saunders Company, Ltd. 1959.

This is certainly an original idea. After some fifteen pages devoted to nutrition, metabolism and growth, with food-charts and diet-lists, the book consists essentially of a large number of simply and skilfully drawn diagrams of the various systems, respiratory, cardiovascular, gastro-intestinal and so on, *not* to be put direct into the patient's hands, but to be used by the doctor to explain how a disease causes symptoms, how it may progress or heal, and what can be done by medical or surgical treatment. It is suggested also that lantern slides, made from these diagrams, would be useful to a doctor lecturing to a lay audience, particularly if he is himself a poor draughtsman. The authors have been careful, in illustrating the increasing activities of growing children, not to be tied to a time-table, and they have deliberately omitted the complications of disease, except for perforation in appendicitis. The word "cancer" is nowhere used, but there is a single page, suitable to be shown to selected patients or their relatives, to illustrate the difference, namely the presence or absence of an enclosing capsule, between a benign and a malignant tumour. The self-examination of the breast is not convincing and could be greatly improved. The index is good.

This book might be very useful as an aid to the explanation of such things as coronary occlusion, allergy, the Rh factor and the menstrual cycle.

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The increasing proportion of older people in the population brings sociological and medical problems into sharp focus.

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Die Speicheldrüsen des Menschen. By Sigurd Rauch, Dr. Med., Dr. Phil., Dr. ès Lettres. (Pp. xii + 507; illustrated. DM 79) Stuttgart: Georg Thieme Verlag. 1959.

This monograph is the most comprehensive one yet prepared on the salivary glands and is likely long to remain the standard work on the subject. It is divided into three major sections—each with appropriate subsections and chapters. The first section is devoted to the morphology and embryology of the glands, the next to their physiology and the biochemistry of their secretions, and the last to their pathology and clinical disorders. This final section, which forms the major part of the book, deals successively with the inflammatory, metabolic and neoplastic diseases of the glands. Each chapter is followed by its bibliography, and the many thousand references included must cover virtually all the publications hitherto made on the subject. This monograph should prove of great value to physiologists, physicians and dentists.

This scholarly work reflects great credit on the author, and with him may be associated many colleagues at the University of Geneva who helped him in the preparation of this encyclopædic monograph. The format of the book has the high standards now associated with this publisher.

A Synopsis of Obstetrics and Gynæcology. By Aleck W. Bourne, M.A., M.B., B.Ch.(Camb.), F.R.C.S.(Eng.), F.R.C.O.G. 12th ed. (Pp. vii + 632; illustrated. 35s.) Bristol: John Wright & Sons Ltd. 1959.

A book which has reached its twelfth edition during its author's lifetime may fairly be said to have achieved the fame of a classic. When it is further appreciated that the first edition made its appearance in 1913, the extent of Mr. Aleck Bourne's achievement with his "Synopsis of Obstetrics and Gynæcology" is all the more remarkable.

In the preface, Mr. Bourne modestly claims that his book is not a textbook but is meant as a companion to more serious and detailed reading of both subjects.

Perhaps the most striking features of the book are its completeness and the grasp it shows of the most modern and up-to-date knowledge. An excellent balance is obtained in the various topics discussed with the proper emphasis on the things which are common and therefore the most important to the student.

Primarily intended as a *vade mecum* and book of reference for medical students, the book will commend itself to many postgraduates for its clarity, brevity and completeness.

Therapeutic Radiology. Rationale, technique, results. By William T. Moss, M.D. (Pp. 403; illustrated. 93s. 6d.) St. Louis: The C. V. Mosby Company. London: Henry Kimpton. 1959.

This new textbook of therapeutic radiology fills a definite need for an authoritative work for the student radiotherapist and for surgeons and other specialists who treat malignant disease and need a knowledge of the indications or otherwise of radiotherapy in the various regions of the body. At the same time it adds a thoroughly readable book to the library of the specialist radiotherapist.

The author does not attempt an exhaustive description of the whole field. Details of treatment are limited to the more successful and well-tried methods, and the discussions are mainly concerned with accepted lines of treatment. The relative advantages of super-voltage therapy or treatment in the 250 kV range are discussed. Throughout the book it is always stressed that the well-being of the patient as a whole must never be forgotten while concentrating on the disease.

A description of the effects of radiation on normal tissues and the relative sensitivity of the type of carcinoma cell precedes the discussion on treatment of individual organs. The value of irradiation, either alone or in combination with surgery, is assessed in the various regions of the body and for the different stages of growth, where appropriate.

There is no description of radiological physics, a knowledge of this subject being assumed, nor is there any detail of treatment by radioisotopes. The indications for isotope therapy and a discussion of its value compared with conventional irradiation are mentioned under the appropriate headings.

Therapeutic Electricity and Ultraviolet Radiation. Edited by Sidney Licht, M.D. (Pp. xii + 373; illustrated. $10.) New Haven, Conn.: Elizabeth Licht, Publisher. 1959.

This is the fourth volume of the Physical Medicine Library edited by Dr. Licht and maintains the high standard set by previous volumes.

Licht gives a comprehensive and fascinating account of the history of electrotherapy and ultraviolet therapy. Reiner contributes an excellent and beautifully clear chapter on the technical aspects of electrical stimulation of muscle which should be of great value to students of physical medicine and physiotherapy.

Stillwell's chapter on the clinical aspects of electrical stimulation is well reasoned, commendably critical and gives a fair picture of the indications and limitations of this controversial therapeutic measure.

Harris deals well with iontophoresis—his chapter should do much to put this overprescribed technique in its place. Ultraviolet light is exhaustively treated: instrumentation is discussed by Anderson, the physiological effects by Fischer and Solomon and the clinical aspects by Scott. The combined effect of these three chapters is to place the application and rationale of ultraviolet light on a sound scientific basis.

Finally, Obrosow of Moscow writes on the use of electrosleep in psychiatric conditions, which opens up a new and fascinating prospect in medicine.

This book is well produced, well documented and an important contribution to the subject. It can be thoroughly recommended.

The Principles and Practice of Electrotherapy and Actinotherapy. By Bryan O. Scott, M.R.C.S., L.R.C.P., D.Phys.Med. (Pp. viii + 314; illustrated. 27s. 6d.) London: William Heinemann Medical Books Ltd. 1959.

This book is an attempt to provide the physiotherapist and trainee physical medicine specialist both with the basic physics required for an understanding of electrotherapy and ultraviolet light and with a description of techniques of application and their clinical indications and effects.

The chapters on physics are well done and provide probably the best available introduction to the subject. The author states in his first chapter that physics is the foundation of physiotherapy and recommends a wide and accurate knowledge of physics. In these days of more active physical treatment with less bias towards passive therapy, this statement is at least arguable, but it is surprising to find the author refusing to describe circuits for electronic stimulators on the grounds that "simplified versions are likely to be erroneous", yet the Faradic coil which is not used now in an up-to-date department is described in detail.

The chapter on electrophysiology is oversimplified and likely to confuse. The place of ultrasonics and iontophoresis is overstated and convincing evidence for their use is not adduced.

The chapters on short-wave diathermy and ultraviolet light are well done and that on dangers of electrical treatments particularly good.

Undoubtedly this book fills a gap and will be of help to students of physical therapy, but it is to be hoped that in the next edition, the author will reconsider the style of writing and the emphasis he has placed on the different aspects of his subject.

Automatic Ventilation of the Lungs. By William W. Mushin, M.A., M.B., B.S., F.F.A. R.C.S., F.F.A. R.A.C.S., L. Rendell-Baker, M.B., B.S., F.F.A. R.C.S., and Peter W. Thompson, B.A., M.B., B.Chir., F.F.A. R.C.S. (Pp. xvi + 349; 191 illustrations. 47s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

The manual control of a patient's respiration is an everyday occurrence, not only as an essential feature of modern anæsthetic technique, but also as an important part of the treatment of respiratory failure, due, for example, to poliomyelitis or narcotic poisoning, and to facilitate this control many types of automatic ventilators have been devised.

As practising anæsthetists the authors of this excellent and timely book are concerned chiefly with those machines designed for, or easily adaptable to, use in the operating theatre; cuirasse and tank type ventilators are outside their terms of reference.

An excellent review of the physiological principles and clinical aspects of controlled ventilation is followed by an exposition of the physical principles involved in ventilator design. Particular attention is given to the pattern of gas flow, volume and pressure produced by the various types of ventilators, and how these patterns are modified by the patient's air passages. Inspiratory and expiratory phases are considered separately and the factors affecting cycling are elucidated.

The practical application of these principles is then exemplified and the greater part of the book is devoted to detailed and well-illustrated descriptions of the many ventilators which have been produced both in this country and abroad.

These are classified primarily by their method of cycling, and a detailed functional analysis in physical terms accompanies the description of each machine, but reports on their clinical usefulness are not given, although the designer's main purpose is mentioned in some cases.

Useful information on inflating valves, ventilation nomograms, hand "resuscitators" and apparatus for measuring gas flow is also included in this invaluable reference book.

It deserves to be closely studied by all anæsthetists and physicians who employ machines for ventilating a patient's lungs, and provides salutary reading for those who feel the urge to design, make or modify an apparatus of this kind.

Heavy Metals and the Brain. By John N. Cumings, M.D., M.R.C.P., (Pp. vii+161. 32s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

This book is divided into three parts dealing with copper, mercury and lead in that order. The main section of the book is concerned with a single rare disease, hepatolenticular degeneration, and copper metabolism; the other two metals occupy less than half the text between them. Professor Cumings is well known for his important work on the role of copper in the pathogenesis of Wilson's disease and on the use of BAL in therapy. It is, therefore, perhaps a pity that he has attempted to cover the whole literature on these subjects, much of which is of purely historical interest, rather than to concentrate his energies on a critical review of the more important recent additions to knowledge enlivened by his own experience. In the section on Wilson's disease, for instance, little mention is made of some of the main unsolved problems such as the poor correlation between biochemical and clinical response to treatment. No attempt has been made to explain his opinion that BAL is so much to be preferred to penicillamine as a therapeutic agent when it is known to be much inferior as a cuprurectic. The stress laid on conclusions reached as a result of salting out the serum proteins is also surprising in view of the superiority of electrophoretic procedures. However, despite these shortcomings this book will be of value to research workers in this field though it may well be of too specialised a nature for the general reader.

An Introduction to Medical Genetics. By J. A. Fraser Roberts, M.A., M.D., D.Sc., F.R.C.P. 2nd ed. (Pp. x+263; 107 illustrations. 35s.) London: Oxford University Press. 1959.

Like the first (1940) edition, this book almost excludes references to plant and animal genetics and exemplifies genetical principles on clinical material. The mathematical methods used are also kept simple. While this approach may commend itself to some clinicians it has the inherent weakness of excluding any results derived from genetical experimentation while depriving itself of the more rigorous inductive methods of statistics, which alone can be a substitute for the experiments which one cannot perform in man.

Nevertheless a considerable sector of our knowledge of medical genetics has been covered. The book deals with the material basis of inheritance, dominant, recessive, intermediate and sex-linked inheritance; further multiple allelism, blood group genetics, linkage, developmental genetics, multifactorial inheritance and with genetical prognosis. Added to this is a brief treatment of some anomalies of chromosome mechanism and intersexuality. (The cytological causation of mongolism was discovered after the manuscript went to print.)

The book does not deal with all the hereditary conditions which may turn up in medical practice, but it succeeds in answering many questions which the clinician might ask or might be asked by his patients, and also provides guidance to the specialist literature. It would be possible to quarrel with some of the statements in the text, but the merit of the book is that it acquaints medical people with the principles of a genetical approach. It may also dispel some current superstitions and it succeeds in not claiming too much for genetical factors in the causation of disease.

Principles and Practice of Obstetric Anæsthesia. By J. Selwyn Crawford, M.B., Ch.B., D.A.(England), F.F.A. R.C.S. (Pp. 128; 2 illustrations. 20s.) Oxford: Blackwell Scientific Publications. 1959.

During the past few years there has been a noticeable re-awakening of interest in the problems of anæsthesia for obstetrics, chiefly because the considerable overall fall in maternal and infant mortality and morbidity has made more obvious those cases where anæsthesia cannot escape a causal responsibility.

Dr. Crawford's purpose in this timely monograph is to review the considerable recent literature—to which he has made stimulating contributions; to evaluate the analgesic and anæsthetic methods currently employed in this country; and to draw attention to some possible deficiencies in the teaching and organization of anæsthesia for obstetric cases.

He has been broadly successful in all these objectives, but it is perhaps inevitable that any up-to-date work about a subject where ideas and techniques are rapidly changing will describe methods which have yet to stand the test of time. Not everyone, for example, would agree "that sufficient evidence now exists to favour the teaching that levallorphan be given with every dose of pethidine"; neither has the value of "hypoæsthesia" or "ataralgesia" as the sole analgesic method for forceps delivery yet received adequate clinical corroboration.

There are excellent sections on the placental transmission of drugs, on the respiratory mechanisms of the newborn and on infant resuscitation, all of which review recent work not found in current anæsthetic textbooks, and in which the author draws attention to the gaps in our knowledge with many pertinent questions.

This is a stimulating book which reflects much current thinking, and though all readers may not agree with some of the views expressed, no one interested in this still controversial subject can fail to profit by reading it.

A Synopsis of Anæsthesia. By J. Alfred Lee, M.R.C.S., L.R.C.P., M.M.S.A., F.F.A. R.C.S., D.A. 4th ed. (Pp. 616; illustrated. 27s. 6d.) Bristol: John Wright & Sons Ltd. 1959.

An extensive revision, new sections on halothane, the phenothiazine derivatives and induced hypothermia, together with a fuller treatment of obstetric and thoracic anæsthesia and the therapeutic applications of anæsthetic techniques, have all combined to swell the latest edition of this well-known work by over 120 pages.

Although by its size, contents and status, it now rivals many textbooks, it is accurately described by its title, and remains true to the author's original purpose of providing a summary of current teaching and practice.

Covering such a large field and with the compressed and slightly dogmatic style inevitable in a work of this kind, it is a remarkable achievement that there are so very few statements to which exception might be taken. Even these should cause no harm if Dr. Lee's preface is heeded and the reader refers to the standard textbooks, and to the many recent papers to which the references are given.

A comprehensive index with over 4,500 entries greatly increases the value of this excellent book, which no doubt will be as deservedly popular with post-graduate students—and with their teachers—as have been the earlier editions.

Synopsis of Treatment of Anorectal Diseases. By Stuart T. Ross, M.D., F.A.C.S., F.I.C.S. (Pp. 240: 79 illustrations. 48s. 6d.) St. Louis: The C. V. Mosby Company. London: Henry Kimpton. 1959.

This an excellent book; it achieves all that it sets out to do. The diagnosis and treatment of all anorectal diseases and of the three commonest colonic disorders (carcinoma, diverticulitis and ulcerative colitis) is presented in an accurate and concise manner, making this synopsis an excellent reference-book for the practitioner, and a first-class factual account of the subject for the interested medical student or house-officer.

One can find very few things with which to join issue; almost all the procedures advised are routine in this country. It is, however, surprising that anterior resection is not advised as a method of treatment of any rectal cancer. The "new" anatomy does not seem to have been accepted; the lower border of the internal sphincter is still called the subcutaneous external sphincter ani—though this is mainly of academic interest.

Though it does not set out to be a book on operative surgery, the method described for performing Thiersch's operation is not ideal.

Diagrams, pictures and radiograms are useful and informative, except the illustration of Hirschsprung's disease. The text is well set out and easy to read. This book, like so many American books, is expensive.

With these few criticisms, one can thoroughly recommend this synopsis.

The New Frontier: Man's Survival in the Sky. By K. G. Williams, M.R.C.S., Assoc.M.I. Mech.E. (Pp. vii+161; illustrated. 21s.) London: William Heinemann Medical Books Ltd. 1959.

The author gives to this book the easy style which can only come from someone who is able to draw on considerable length of experience in his subject. His pen takes the reader effortlessly, division by division, throughout the whole field of one of the youngest, though extensive, offshoots of medicine—namely, aviation medicine.

Although technical terms have been avoided, thus making the text entirely comprehensible to a layman, there is an ample depth of detail to provide the general practitioner with a comprehensive general knowledge of the physiology involved in modern air travel of all kinds.

For the perceiving reader it must become apparent that the last few years have produced, from extensive research, much knowledge and experience that can be drawn upon for application in allied man/machine fields. The chapters on forces involved in crashes, and protection therefrom; also instrumentation and control layout are but two examples from which the motor industry could well learn.

The book is brought right up to date with a comprehensive survey of the difficulties confronting man in his conquest of space, and the hazards awaiting him when he gets there.

In conclusion, this is a non-clinical book from an acknowledged medical authority who has specialized in research into aviation medicine. The facts are presented accurately in a very pleasing style which should appeal to lovers of science fiction as well as to those who wish to broaden their horizon in aviation medicine.

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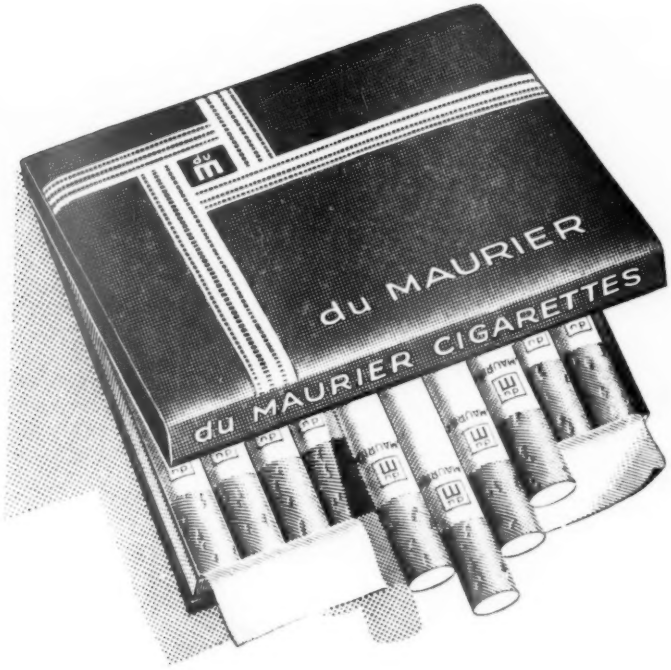

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